Neuregulin Signaling in the Tumor Microenvironment

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Abstract

Neuregulins, members of the largest subclass of growth factors of the epidermal growth factor family, mediate a myriad of cellular functions including survival, proliferation, and differentiation in normal tissues through binding to receptor tyrosine kinases of the ErbB family. However, aberrant neuregulin signaling in the tumor microenvironment is increasingly recognized as a key player in initiation and malignant progression of human cancers. In this chapter, we focus on the role of neuregulin signaling in the hallmarks of cancer, including cancer initiation and development, metastasis, as well as therapeutic resistance. Moreover, role of neuregulin signaling in the regulation of tumor microenvironment and targeting of neuregulin signaling in cancer from the therapeutic perspective are also briefly discussed.

1.1 Introduction

Over the past two decades, tumor has increasingly been recognized as organ that results from the co-evolution of malignant cells and their direct environment [1, 2]. The tumor microenvironment (TME) encompasses extracellular matrix (ECM) and various non-transformed cells including fibroblasts, immune infiltrates, and vascular vessels recruited from nearby local or distant tissues [3]. Through providing matrices, cytokines, growth factors, as well as vascular networks for nutrient and waste exchange, the TME plays an essential role in tumor initiation, progression, invasion, metastasis, and resistance to therapy [4].

Cumulative studies have demonstrated that the cross talk between cancer cells and their TME

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involves reciprocal juxtacrine and paracrine signaling pathways. Among them, neuregulin (NRG) signaling has long been recognized as an important player in regulating tumor progression [5]. Neuregulins (NRGs) are members of the largest subclass of polypeptide factors that bind to receptor tyrosine kinases of the ErbB family and mediate a myriad of cellular functions including survival, proliferation, and differentiation in normal tissues [6]. However, there is mounting evidence that dysregulated neuregulin signaling plays important role in initiation and development of a variety of human cancers via regulating cancer cells and/or the TME [7, 8]. Thus, the neuregulin signaling is emerging as therapeutic target in exploring novel strategy against cancer [9, 10]. The aim of this chapter is to discuss how neuregulin signaling takes an important part in regulating the tumor biology. We also address the targeting of neuregulin signaling in cancer from the therapeutic perspective.

1.2   Overview of Neuregulin Signaling

NRGs are a family of structurally related signaling proteins that mediate cell–cell interactions in a broad spectrum of tissues including breast, heart, nervous system, and others [11, 12]. Identified independently over two decades ago by several different research groups, these peptide growth factors were originally described as neu differentiation factor (NDF) [13], heregulins (HRGs), acetylcholine receptor-inducing activity (ARIA) [14], glial growth factors (GGFs) [15], and sensory and motor neuron-derived factor (SMDF) [16]. NRG was first characterized in rat and human as a putative ligand for the ErbB2 [13, 17, 18]; however, it was later showed that the actual receptors of NRG were ErbB3 and ErbB4 [19, 20]. Currently, 4 NRG genes, NRG-1, NRG-2, NRG-3, and NRG-4, encoding more than 30 different isoforms through multiple promoter usage and alternative splicing, have been described [7, 21–24]. Moreover, studies are continually revealing that the family of NRGs may be larger than currently known [25–27].

The structures and distribution of different isoforms of NRG had been well reviewed [8, 11]. All NRGs share a typical EGF-like domain, an important structure which it alone is sufficient for receptor binding and the activation of intracellular signaling pathways. This extracellular domain contains about 50 amino acids and is characterized by 3 pairs of cysteines that are important for its tertiary structure and biological function. The differences in EGF-like domain define the α and β isoforms of NRG. Among the four members of NRG gene, NRG-1 is the best characterized one whose biological functions had been extensively studied. Transcribed from the same NRG-1 gene located on human chromosome 8p12, the isoforms of NRG-1 mRNA differ in their coding segment composition due to initiation of transcription from different NRG-1 gene promoters and alternative splicing which give rise to six types of NRG-1 (types I, II, III, IV, V, and VI). These different types of NRG-1 are also divided based on the differences in their extracellular amino-terminal domains with types I, II, IV, and V sharing an immunoglobulin-like (IgG-like) domain followed by a glycosylation-rich region (type I) or a GGF-specific (kringle) domain (type II) while type III of NRG-1 containing a cysteine-rich domain (CRD) that loops back intracellularly along with its N-terminal sequence. In addition, whether the isoform is initially synthesized as a transmembrane or nonmembrane protein adds more dimensionality to different isoforms of NRG. The human NRG-2 gene located on chromosome 5q31.2 encodes six isoforms of NRG-2 (α, β, αν, βν, α*1, and α*2) [21, 28–30]. The human NRG-3 and NRG-4 genes were mapped to chromosome 10q23.1 and 15q24.2, respectively [31, 32]. While the NRG-1 transcripts were evidenced to be broadly expressed in multiple tissues, both NRG-2 and NRG-3 were found to be mainly expressed in the nervous system. Although the expression of NRG-4 mRNA has only been detected in the pancreas and to a lesser extent in muscle [24], NRG-4 protein expression was found in bladder as well as prostate cancer [32, 33]. Structurally, NRG-4 is distinct from other NRGs, which contain no recognizable motifs other than the EGF-like

domains. Most NRGs are synthesized as large transmembrane precursor proteins with the EGF-like domain connected to the transmembrane domain by a juxtamembrane linker. These NRGs can be activated and released from the membrane through proteolytic processing, which has also been extensively studied and reviewed [34–37].

In the current body of knowledge, NRGs mainly elicit their biological functions via binding of ErbB3 or ErbB4 in an autocrine, paracrine, or juxtacrine way (Fig. 1.1) [5, 38, 39]. The ErbB subfamily of transmembrane receptor tyrosine kinases (RTKs) consists of four closely related transmembrane receptors: ErbB1 (also known as EGFR or HER1), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4) [40]. Among all four ErbB subfamily members, NRGs can directly bind to the ErbB3 and ErbB4 receptors. All products of four NRG genes can bind ErbB4, whereas only NRG-1 and NRG-2 proteins can bind ErbB3 [41, 42]. Binding of ligands to the extracellular domain of ErbB3 or ErbB4 induces the formation of kinase active homo- or hetero-oligomers, which further induces transphosphorylation of the ErbB dimer partner and stimulates down-stream intracellular pathways including RAS/RAF/MEK/ERK, PI3K/Akt/mTOR, Src kinases, and JAK/STAT [43, 44]. To date, there is no known ligand for ErbB2; however, ErbB2 is constantly in a conformation that resembles a ligand-activated state and favors dimerization [45, 46]. Unlike other ErbB receptors, ErbB3 can bind ATP and catalyze autophosphorylation, whereas it has a weak kinase activity [47]. Interestingly, ErbB3 possesses most tyrosine residues in its intracellular domain ready to be phosphorylated. It must interact with other RTKs to exhibit its biological functions [48]. Among many interactive partners of ErbB3, ErbB2 is the most important one [49]. Upon ligand binding, ErbB3 triggers the formation of ErbB2/ErbB3 heterodimer, in which ErbB3 benefits from ErbB2's strong kinase activity for phosphorylation on its intracellular tyrosine residues. Thus, the "dumb" ErbB3 (weak kinase activity, but has ligands) and the "deaf" ErbB2 (no known ligand, but has kinase activity) make a perfect sense to form a potent ErbB2/ErbB3 heterodimer leading to activation of the downstream signaling pathways (Fig. 1.2) [42]. Accordingly, co-expression of
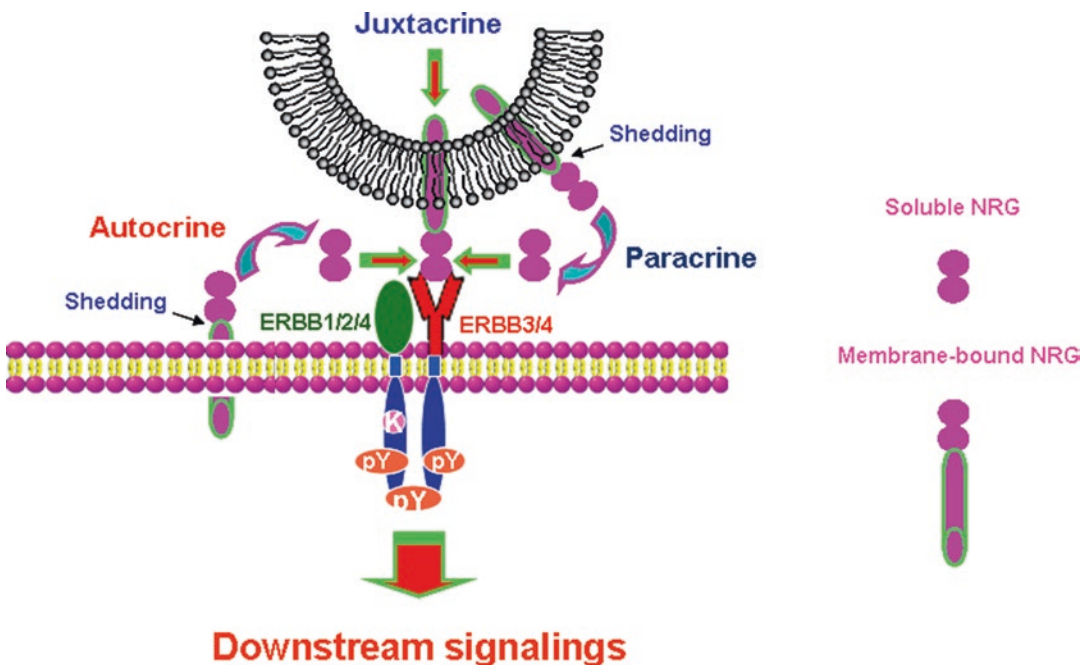
Fig. 1.1 Schematic diagram of acting models of NRGs
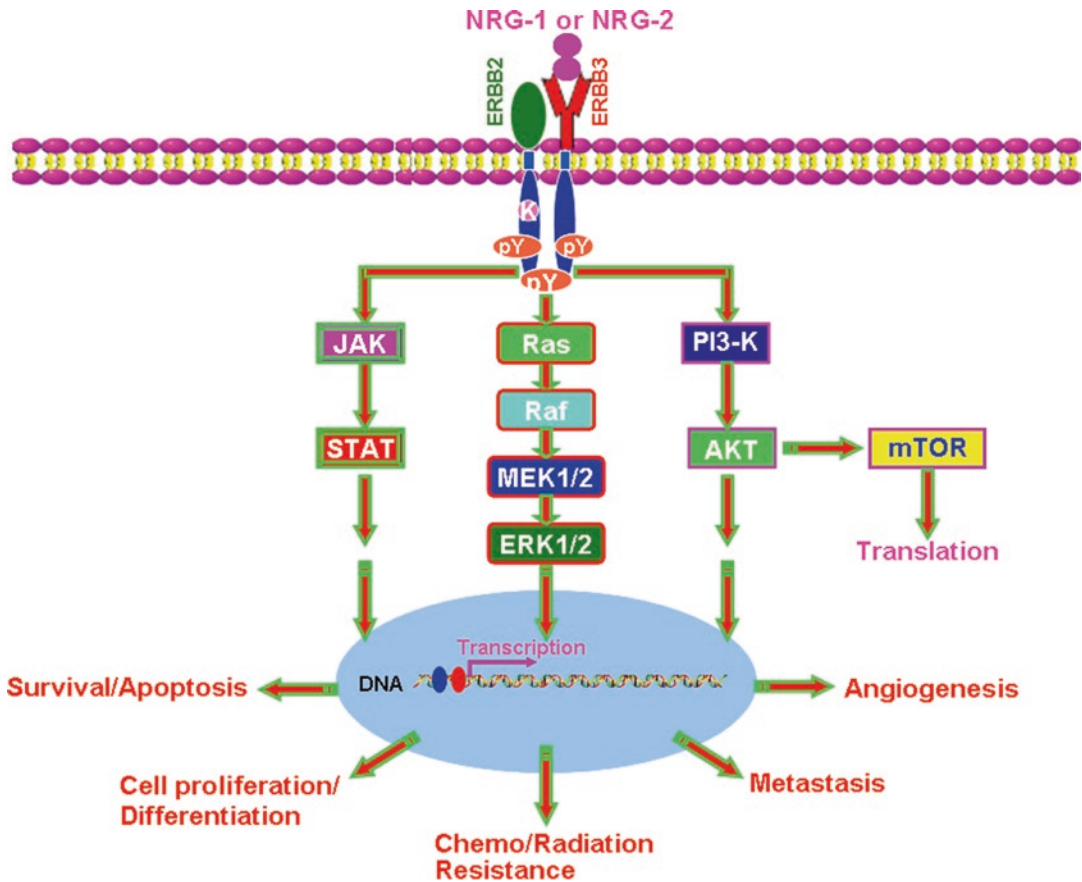
Fig. 1.2 Schematic diagram of NRG signalings and their biological consequences

ErbB3 and ErbB2 in normal or cancer tissues is frequently observed [50, 51], and ErbB3 has been increasingly evidenced to play a critical role in ErbB2-mediated cancer development as well as therapeutic resistance [52–56].

1.3 Role of Neuregulin Signaling in Hallmarks of Cancer

NRG is initially identified as an important regulator in the development of nervous system [57]; however, NRG-induced signaling has also been shown to play a pivotal role in a wide variety of tissues, including breast [58, 59], heart [60], lung [61], muscle [62], and stomach [63]. Given the importance of ErbB receptors in hallmarks of cancer [64, 65], it has been evidenced that aberrant activation of the NRG signaling acts as a key

player in the development and progression of various human cancers, which will be discussed in detail in the following section of this chapter (Table 1.1) [5, 7, 8].

1.3.1 Role of Neuregulin Signaling in Cancer Initiation and Development

Cancer is a genetic disease. Several lines of evidence indicate that tumorigenesis is a multistep process and that these steps reflect genetic alterations that drive the progressive transformation of normal cells into highly malignant derivatives [66]. Among the eight distinctive and complementary capabilities—hallmarks of cancer—enabling tumor growth and metastatic dissemination proposed by Hanahan et al. [2, 66],

Table 1.1 Neuregulin genes, products, and expression in human tumors

NRG gene	Location on chromosome	Protein product	Type of tumor	Representative references
NRG-1	8p12	NRG-1/HRG-1/NDF/ARIA/GGF/SMDF	Breast cancer	Aguilar et al. [83]
			Colon cancer	Venkateswarlu et al. [124]
			Endometrial cancer	Srinivasan et al. [148]
			Gastric cancer	Noguchi et al. [63]
			Glioma	Westphal et al. [139]
			Hepatocellular carcinoma	Hsieh et al. [149]
			Lung cancer	Gollamudi et al. [106]
			Medulloblastoma	Gilbertson et al. [150]
			Melanoma	Buac et al. [151]
			Ovarian cancer	Gilmour et al. [152]
			Pancreatic cancer	Kolb et al. [154]
			Papillary thyroid cancer	Fluge et al. [155]
			Prostate cancer	Leung et al. [157]
			Squamous cell carcinomas of the head and neck	Shames et al. [158]
			Vestibular schwannoma	Hansen et al. [141]
NRG-2	5q31.2	NRG-2/HRG-2	Breast cancer	Carraway et al. [21]
			Schwannoma	Stonecypher et al. [142]
NRG-3	10q23.1	NRG-3/HRG-3	Breast cancer	Hijazi et al. [159]
NRG-4	15q24.2	NRG-4/HRG-4	Bladder cancer	Memon et al. [32]
			Prostate cancer	Hayes et al. [33]

NRG neuregulin, *HRG* heregulin; NDF, neu differentiation factor,;*ARIA*, acetylcholine receptor-inducing activity, *GGF*, glial growth factor, *SMDF*, sensory and motor neuron-derived factor

sustaining proliferative signaling is fundamental in cancer initiation and development.

In normal tissues, the production and release of growth-promoting signals governing cell growth and proliferation is strictly controlled, thereby ensuring a homeostasis of cell number and thus maintenance of normal tissue architecture and function. In contrast, malignant cells acquire the ability to sustain proliferative signaling via accumulating genetic as well as epigenetic alterations. The mitogenic signals are largely conveyed by growth factors that bind cell surface receptors such as RTKs, typically containing intracellular tyrosine kinase domains. The RTKs proceed to elicit signals via branched intracellular signaling pathways that regulate progression through the cell cycle as well as cell growth [67, 68].

Over the past several decades, it has become evident the ErbB subfamily members of RTKs have a prominent role in the initiation and development of several types of cancer. The evidence for a role of ErbB receptorsin cancer was first inferred from a study on ErbB2, a human ortholog of rat Neu, as forced overexpression of human ErbB2 was shown to transform diploid cells [69]. Almost at the same time, the *EGFR* was initially identified as an oncogene owing to its homology to *v-erb-B* [70]. Overexpression of wild-type Neu or ErbB2 under the control of a mammary-specific promoter was latterly shown to lead to metastatic mammary tumors in transgenic mice [71, 72]. Consistently, the amplification and/or overexpression of ErbB2 was found to be significantly and independently associated with a worse prognosis for breast cancer patients [73, 74]. Less frequent activating mutations of *ErbB2* in several cancer types without gene amplification were further unveiled [75]. Comparably, the causal role of EGFR in tumorigenesis of a rela-

tively broad spectrum of cancers was well recognized thereafter its first identification as oncogene [76–78]. Although mutations in both *ErbB3* and *ErbB4* were identified in human cancers [79–81], the involvement of ErbB3 and ErbB4 in cancer was mainly revealed as partners in promoting signaling from EGFR and ErbB2 currently [44].

As aforementioned, most of the time, homo- or hetero-dimerization of ErbB receptors triggered by binding of ligand is prerequisite for fulfilling their biological function. Ever since NRGs were identified as the ligands of ErbB3 and/or ErbB4, the role of NRGs in cancer initiation and development has attracted much research interest. While forced overexpression of NRGs in the mammary gland of transgenic mice was shown to provoke the development of breast adenocarcinomas [82], NRGs were also evidenced to function as potent stimulators of proliferation of both malignant human breast and ovarian epithelial cells in vitro [83]. Moreover, development of an autocrine NRG signaling loop results in transformation of breast epithelial cells into malignant derivates [84]. Consistently, NRG is overexpressed in about 30% of breast cancer biopsies that do not overexpress ErbB2, and this overexpression is sufficient to promote tumorigenesis and metastasis of breast cancer cells [85, 86]. In addition to growth factors, the development of breast cancer is also regulated by a plethora of signals mediated by steroid receptors such as estrogen receptor (ER) and progestogen receptor (PR) [87, 88]. Importantly, although NRG was showed to induce an estrogen-independent phenotype of breast cancer cells [85, 89], the interactions between progestins and NRG signaling pathways were unveiled in the development of mouse mammary adenocarcinomas [90]. NRG not only induces transcriptional activation of the progesterone receptor via an ErbB2-dependent manner in breast cancer cells [91] but also drives breast cancer growth through the co-option of progesterone receptor signaling [92]. Mechanistically, while the extracellular region of NRG was shown to promote mammary gland proliferation and tumorigenesis [93], a recent study demonstrated that the Ig-like region of NRGs may exert an important role in their capa-

bility to activate ErbB receptors and mitogenic responses [94]. Consequently, circulating NRG1 has been demonstrated to be additional biomarkers indicative of prognosis and outcomes for breast cancer patients [95].

Lung cancer remains the most commonly diagnosed cancer and the leading cause of cancer-related deaths worldwide [96]. Of all pathological types, non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers [97]. Extensive genomic characterization of NSCLC has led to the identification of molecular subtypes of NSCLC that are oncogene addicted, including overexpression and/or activating mutations in epidermal growth factor receptor (EGFR) [98]. However, there is mounting evidence that substantial molecular and clinical heterogeneity exists within oncogenic driver-defined subgroups of NSCLC [99, 100]. In comparison with a higher prevalence of EGFR mutations in NSCLC [78], the aberrations of other ErbB subfamily members have also been observed in NSCLC but with a relative low frequency [101]. The mutations of ErbB2, ErbB3, and ErbB4 were reported to occur in about 4% [102], 1% [79], and 5.4% [103] of human primary lung tumors, respectively. Nevertheless, in addition to EGFR, the overexpression of other ErbB subfamily members was frequently detected in NSCLC [102, 104]. While ErbB2, ErbB3, ErbB4, and NRG were found to be differentially expressed in normal bronchial epithelial and NSCLC cell lines [105], an autocrine activation of ErbB2/ErbB3 receptor complex by NRG-1 was further unraveled in NSCLC cells [106]. These studies raised the potential role of NRG signaling in initiation and development of NSCLC. More importantly, through transcriptome sequencing of 25 lung adenocarcinomas of never smokers, a novel somatic gene fusion, *CD74–NRG1*, was identified [107]. The *CD74–NRG1* was demonstrated to give rise to the extracellular expression of the EGF-like domain of NRG1 III-β3 which acts as the ligand for ErbB2/EebB3 receptor complexes. Thereafter, *NRG1* fusions were reported in different populations with different frequencies in NSCLC [108–111]. In addition to canonical NRG signaling, a recent study demonstrated that EGF and NRG may

induce phosphorylation of ErbB3 by EGFR using distinct oligomeric mechanisms which even broadens our understanding of NRG signaling in cancer development [112]. The increasing recognition of the role of NRG signaling in lung cancer has raised the possibility that specific inactivation of NRG signaling may have therapeutic potential in this malignant disease [113]. More detailed information regarding the NRG signaling-targeted therapy for cancer treatment will be discussed in the rear part of this chapter.

Dysregulated ErbB signaling has also been reported to be involved in development of neoplasms of gastrointestinal tract, which mainly include esophageal carcinoma, gastric cancer, liver cancer, colorectal cancer (CRC), and pancreatic cancer accounting for more than 26% and 35% of all new cancer cases and deaths worldwide [44, 96]. Overexpression of ErbB2 in gastric cancer was firstly reported in 1986 [114]. Thereafter, accumulated data indicates the association of ErbB2 and/or ErbB3 overexpression with poor prognosis of patients with this disease [115–117]. While HRG-α was showed to affect epithelial cell proliferation through mesenchymal–epithelial interaction in the gastric mucosa [63], an interesting study demonstrated that overexpression of NRG1 could promote progression of gastric cancer by regulating the self-renewal of cancer stem cells [118]. In contrast to EGFR and ErbB2, which have been widely studied in CRC [119], the role of ErbB3 and ErbB4 in CRC is largely underestimated previously. Although the expression of ErbB3 in CRC was reported to range from 36 to 89% [120, 121], the information regarding its prognostic role in CRC was ever limited. This situation changed when two groups reported that ErbB3 overexpression was significantly associated with decreased time to CRC progression [122, 123]. Actually, autocrine heregulin has been demonstrated to generate growth factor independence and block apoptosis in CRC cells as early as in 2002 [124]. Interestingly, bone marrow-derived mesenchymal stem cells (MSCs) in TME were evidenced to promote CRC progression through paracrine NRG1/ErbB3 signaling [125]. In addition to acting on cancer cells themselves, NRG signaling

was shown to induce expression of vascular endothelial growth factor (VEGF) in colon cancer cells, which might further affect the growth of colon cancer in vivo [126]. ErbB4 is the least recognized ErbB subfamily member. However, phosphorylated ErbB4 and NRG have also been demonstrated to contribute to poorer patient prognosis in CRC [127, 128].

The worldwide mortality of pancreatic cancer ranks the seventh among all cancers in both sexes accounting for about 4.5% of all cancer deaths [96]. Extensive genetic studies have revealed that during the progression of three broad stages of pancreatic cancer, acquired somatic mutations in oncogenes and tumor suppressor genes accumulate and account for initiation and aggressive development of this malignant disease. These mutations occur most frequently in *KRAS*, *CDKN2A*, *TP53*, and *SMAD4* [129–131]. Activating mutations of the *KRAS* oncogene, which encodes a member of the RAS family of GTP-binding proteins, are the most common genetic abnormality presenting in approximately 95% of pancreatic tumors analyzed [132, 133]. In addition, wild-type KRAS is also normally activated in response to the binding of extracellular signals such as growth factors to RTKs [134]. Accumulating evidence shows that the ErbB receptors are overexpressed in approximately 60% of pancreatic cancers [135]. Recently, several studies have uncovered that recurrent gene rearrangements such as *NRG1* fusions are prevalent in patients with *KRAS* wild-type pancreatic cancer [136, 137]. Thus, in a subset of *KRAS* wild-type pancreatic cancer cases, NRG signaling may act as targetable oncogenic driver, providing a potential treatment strategy in this disease [138].

Given the role of NRG in the development of nervous system, it is thus not surprising that aberrant NRG signaling could result in development of glioma and schwannoma [139–142]. Gliomas are the leading cause of death among adults with primary brain malignancies due to lack of effective remedy [143, 144]. In an attempt to search for novel target therapy against glioma, an RNAi-based inhibition of presenilin 2 was demonstrated to inhibit glioma cell growth and invasion via

regulation of NRG1/ErbB signaling [145]. MicroRNA is emerging as important player in tumor biology [146]. It was revealed that the expression of miR-125a-3p was significantly decreased in malignant glioma and lower expression of miR-125a-3p was associated with a poor prognosis of patients with glioblastoma. Further mechanistic study suggested that miR-125a-3p might perform an important role in development of glioma via direct targeting of NRG-1 [147]. In addition to aforementioned cancer types, the aberrant NRG signaling was also involved in development of many other cancers derived from different tissues as listed in Table 1.1 which will not be discussed in detail [148–159].

1.3.2   Role of Neuregulin Signaling in Cancer Metastasis

Currently, metastatic disease is largely incurable and remains the main cause of cancer-related deaths worldwide [160]. Metastasis is the end result of a multistage process that includes acquisition of invasive phenotype of primary tumor cells, local invasion, intravasation into the blood or lymphatic system, survival in circulation, arrest at a distant organ, extravasation, survival in a new environment, and adaptation and proliferation to form metastases [161]. Each of these steps in the complex metastatic cascade depends on the genetic and epigenetic alterations acquired by primary tumor cells, as well as interactions with the host microenvironment and the immune system [162, 163].

Change in cell phenotype between epithelial and mesenchymal states, defined as epithelial–mesenchymal transition (EMT), has been increasingly recognized as an initial step of tumor metastasis [164]. The EMT program is generally induced in epithelial cells by heterotypical signals, among which the transforming growth factor-β (TGFβ) family of cytokines are the best characterized inducers of EMTs [165]. In addition, RTK signaling has also been shown to play crucial roles in the induction of EMT [166]. NRG-1 was able to enhance motility and migration of human glioma cells via not only activation

of focal adhesion kinase (FAK) [167] but also induction of expression of cell adhesion molecule L1 [168]. While the constitutive activation of ERBB3-dependent signaling driven by an NRG-1/ERBB3 autocrine mechanism was strongly associated with microscopic vascular invasion and poor prognosis of hepatocellular carcinoma (HCC) [149], a recent study further demonstrated that miR-296-5p suppressed EMT of HCC via targeting NRG1/ErbB2/ErbB3 signaling [169].

Metastatic lesions develop from disseminated cancer cells (DCCs) that can remain dormant [170]. Accumulating data suggest that metastatic dissemination often occurs early during tumor formation [171, 172]. Progesterone-induced signaling was shown to trigger migration of cancer cells from early lesions shortly after HER2 activation in a HER2-driven mouse mammary tumor model which exhibited capability for early metastatic dissemination [173]. Using the same mammary tumor model, a subpopulation of $Her^{2+}p\text{-}p38^{lo}p\text{-}Atf2^{lo}Twist1^{hi}E\text{-}cad^{lo}$ early cancer cells with invasive ability to spread to target organs was identified in the early lesions of the transgenic mice [174]. These studies strongly suggested that aberrant ErbB2 signaling played a pivotal role in early dissemination of breast cancer cells. Furthermore, while the NRG expression in breast tumors was evidenced to be associated with lymph node invasion and poor patient outcome, it was demonstrated that NRG expression favored in situ tumor growth, local spreading, and metastatic dissemination via an ERK1/2 kinase-dependent upregulation of collagenase-3 [175].

Tumor-associated macrophages (TAMs), derived from recruited circulating monocytes by a wide variety of growth factors such as colony-stimulating factor 1 (CSF1), are critical for regulating processes of tumor including various steps in the metastatic cascade [176–179]. The first direct evidence for a synergistic interaction between macrophages and tumor cells during cell migration in vivo was provided in 2004 [180]. Macrophages are conventionally subdivided into antitumor pro-inflammatory M1 or pro-tumor immune-suppressive M2 phenotypes; however, the diversity of macrophage types in different tis-

sues and cancers indicates that this classification is an oversimplification [181]. Accumulating data have revealed different TAM behaviors linked to their locations, including migration-associated streaming and perivascular populations [182–184]. Perivascular macrophages are an essential component of structures termed TMEM (tumor microenvironment of metastasis) that consist of a TAM in direct contact with a Mena-overexpressing tumor cell and endothelial cell [185]. While the EGF–CSF1 paracrine loop between the tumor cells and macrophages was shown to mediate pairing and stream formation [186], it was further demonstrated that the hepatocyte growth factor (HGF) supplied by endothelial cells is required for sustained directional migration of both tumor cells and macrophages toward blood vessels [184]. Moreover, the temporal aspects of macrophage subtype specification within primary tumors and the possibility of interconversion among subtypes had been verified by Arwert and colleagues whose study indicate that a unidirectional transition from migratory to perivascular macrophage is required for tumor cell intravasation [187]. Notably, the EGF/CSF-1 paracrine invasion loop has been reported to be triggered by HRG-β1 and CXCL12 [188]. In addition, heregulin/ErbB3 signaling has also been shown to enhance breast cancer cell motility via hypoxia-inducible factor 1α (HIF-1α)-dependent upregulation of CXCR4, the receptor of SDF-1/CXCL12 [189].

The Notch signaling pathway regulates many aspects of cancer biology, including metastasis [190]. Upon ligand binding, the transmembrane Notch receptor is cleaved sequentially, leading to the release of the Notch intracellular domain (NICD). The NICD translocates to the nucleus where it orchestrates the transcription of specific genes. Ligands of Notch receptor expressed by the signal-sending cell are transmembrane proteins of the Delta/Serrate/LAG-2 (DSL) family which comprises three delta-like ligands (Dll1, Dll3, and Dll4) and two jagged ligands (Jagged 1 and Jagged 2) in mammals. It has been demonstrated that tumor-derived Jagged 1 (JAG1) could promote osteolytic bone metastasis of breast cancer by engaging Notch signaling in bone cells

[191]. Interestingly, stimulation of macrophages by tumor cell-derived NRG-1 results in upregulation of JAG1, which in turn enhances transendothelial migration and intravasation of breast cancer cells [192]. The cross talk between different signaling pathways may play a synergistic role in tumor biology. Through a transcriptome meta-analysis, higher number of gene fusions affecting core members of the Hippo pathway, Neurofibromatosis 1 (NF1), and NRG1 genes was shown to be an independent prognostic factor for poor survival in lung cancer [193]. A direct evidence of cross talk between Hippo and NRG signaling in regulating aggressive behavior of tumor cells was provided by Haskins and colleagues, whose study demonstrated that NRG 1-activated ErbB4 interacted with YAP to induce Hippo pathway target genes and promoted cell migration [194].

The dysregulated NRG signaling in development of lung cancer has been described in the front part of this chapter. In respect to metastasis, some significant differences in ErbB family receptor-related abnormalities have been shown in NSCLC brain metastases in comparison with primary lung tumors [195]. As aforementioned, oncogene fusions have increasingly been identified as driver mutations in lung adenocarcinoma. In an attempt to identify druggable oncogenic fusions in invasive mucinous adenocarcinoma (IMA) of the lung, Nakaoku and colleagues found that two oncogenic fusions involving *NRG1* (*CD74–NRG1* and *SLC3A2–NRG1*) occurred mutually exclusive with *KRAS* mutations [196]. The *SLC3A2–NRG1* fusion was further demonstrated to increase cell migration via promoting ErbB2–ErbB3 phosphorylation and heteroduplex formation and activating the downstream PI3K/Akt/mTOR pathway through paracrine signaling [197].

1.3.3 Role of NRG Signaling in Therapeutic Resistance in Cancer

Rapid progress in our understanding of cancer biology has dramatically improved our therapeu-

tic strategies against cancer. In addition to the conventional operations, such as chemotherapy and radiotherapy, molecularly targeted therapies and immunotherapy recently emerge as the principal modes of cancer treatment. However, resistance to these therapies frequently occurs and currently represents a major clinical problem. Therapeutic resistance can be divided into two broad categories: primary (de novo) or acquired. Primary resistance is usually caused by resistance-mediating factors pre-existing in the bulk of tumor cells, which make the therapy ineffective. Acquired resistance can develop during the treatments of cancers that are initially sensitive. Both primary and acquired resistances can occur at many levels, including increased drug efflux and decreased drug influx, drug inactivation, alterations in drug target, processing of drug-induced damage, and evasion of apoptosis [198].

Acquired resistance can arise through therapy-induced selection of a resistant subpopulation of cells that is present in the original tumors with a high degree of heterogeneity [199]. It can also be caused by mutations arising during the treatments, by increased expression of the therapeutic target, as well as through various other adaptive responses such as activation of the compensatory signaling pathways [200].

1.3.3.1 Resistance to Chemotherapy

Chemotherapy, as an important conventional treatment for human cancers, usually induces cancer cell death by cytotoxicity, thereby reducing the tumor bulk [201]. The mechanism of antitumor activity of chemotherapeutic drugs is complex and involves various biological pathways, including apoptosis, autophagy, necrosis, and mitotic catastrophe [202]. Consequently, the mechanisms of chemoresistance are intricate and not fully understood. Taking into consideration that many clinically used chemotherapeutic drugs mainly exert antitumor activity via induction of apoptosis, it is understandable that cancer cells with enhanced survival signaling and/or defects in apoptotic pathways may escape from those therapies [203]. Since the PI3K/Akt pathway is an important survival signaling and readily acti-

vated by RTKs, including ErbB3, it is rational that aberrant NRG signaling may result in chemoresistance in cancer treatment [204]. In an early study, the co-expression of ErbB2 and ErbB3 in human breast cancer cell lines was shown to be associated with an increased resistance to multiple chemotherapeutic agents, such as paclitaxel, doxorubicin, 5-fluorouracil, etoposide, and camptothecin, via activation of PI3K/Akt signaling [205]. In our own attempt to identify the key downstream mediator of ErbB3 signaling that contributed to chemoresistance, we discovered that elevated expression of ErbB3 conferred paclitaxel resistance in ErbB2-positive breast cancer cells via PI3K/Akt-dependent upregulation of Survivin [56]. MSCs are connective tissue progenitor cells that contribute to fibrotic reactions during tissue remodeling and repair in places of wounding and inflammation. In response to chemokines from tumor cells, MSCs are continuously recruited to and become integral components of the tumor microenvironment [206, 207]. MSCs in tumor microenvironment have been shown to influence multiple hallmarks of cancer, including resistance to chemotherapy [208, 209]. More recently, we demonstrated that the aforementioned ErbB2/ErbB3 → PI3K/Akt → Survivin signaling axis underlying paclitaxel resistance in breast cancer cells could also be activated via the paracrine stimulation by MSCs-derived NRG-1 [210]. Doxorubicin is another widely used drug in chemotherapy against multiple types of cancer. It was reported that treatment with doxorubicin resulted in activation of the ErbB3–PI3K–Akt signaling cascade in ovarian cancer cells through transcription-dependent upregulation of NRG1 and specific blockade of ErbB3 enhanced the doxorubicin-induced apoptosis [211]. These data suggest that an activated NRG1/ErbB3 autocrine loop may account for doxorubicin resistance in ovarian cancer cells.

1.3.3.2 Resistance to Targeted Therapy

Multiple processes of cancer initiation and development involve the progressive acquisition of genetic mutations and epigenetic abnormalities in the expression of various genes with highly

diverse functions. Nonetheless, the observation that some cancer cells can seemingly exhibit dependence on a single oncogenic pathway or protein for their sustained proliferation and/or survival has led to a new concept referred to as oncogene addiction [212]. The notion of oncogene addiction reveals a possible "Achilles' heel" within the cancer cells that can be therapeutically targeted [213, 214].

Owing to the improved understanding of the oncogenic driver mutations in NSCLC, targeted therapy has been extensively exploited while combating this malignant disease. Systematic analysis has revealed that almost two-thirds of patients with NSCLC harbor an oncogenic driver mutation, approximately half of whom have a therapeutically targetable lesion [215]. Although treatment with a targeted therapy improves outcomes in patients with NSCLC, responses to the therapeutic agents are generally incomplete and temporary followed by resistance [216]. Cancer cells develop several mechanisms of resistance to targeted therapy, which can be classified as "on-target" or "off-target" [217]. Alterations of the primary target of the drug typically result in on-target resistance [218]. In the circumstance of off-target resistance, activation of collateral signaling events that are parallel to, or downstream of, signaling by the driver oncoprotein bypass the requirement of the driver oncoprotein for cell survival and growth. Among the expanding spectrum of oncogenic driver mutations identified in NSCLC, somatic activating mutations in EGFR are the most common ones occurring in ~16% of patients with advanced lung adenocarcinoma [219]. Currently, two strategies including blocking antibody such as cetuximab and tyrosine kinase inhibitors (TKIs, such as gefitinib, lapatinib, and erlotinib) are mainly used in EGFR-targeted therapy in clinic [220]. Cumulative data have indicated that activation of NRG/ErbB3 signaling is one of the major mechanisms contributing to the resistance to EGFR-targeted therapy [221–224]. It has been reported that MET amplification leads to gefitinib resistance in lung cancer treatment by activating ErbB3 signaling [225]. Besides, NRG/ErbB3 signaling was also shown to induce resistance to lapatinib-mediated

growth inhibition of *ErbB2*-amplified gastric cancer cells and cetuximab-based therapy in colorectal cancer, respectively [226, 227]. The *EML4–ALK* fusion gene was detected in 3% to 7% of patients with NSCLC [228, 229]. It has been demonstrated that crizotinib, an ALK inhibitor, shows remarkable antitumor effect in *EML4–ALK*-positive lung cancer [230]. However, patients receiving treatment with crizotinib eventually acquire resistance to this drug. While paracrine receptor activation by ligands from the microenvironment was demonstrated to trigger resistance to ALK inhibitors in EML4–ALK lung cancer cells [231], an analysis of patient-derived cancer cell further revealed that activation of neuregulin/ErbB3 signaling accounted for crizotinib resistance in EML4–ALK lung cancer [232]. In addition, paracrine effect of NRG1 was also evidenced to drive resistance to MEK inhibitors in metastatic uveal melanoma [233].

The finding that amplification and/or overexpression of ErbB2 occurs in approximately 25% of invasive breast cancer and is significantly associated with a worse prognosis for breast cancer patients has made ErbB2 an attractive therapeutic target [73, 74, 234]. ErB2-targeted therapy in breast cancer is thus another paradigm in cancer research. As the first ErbB2-targeted agent approved by the US Food and Drug Administration (FDA), trastuzumab (also known as Herceptin, a humanized monoclonal antibody against ErbB2) has demonstrated significant activity in the treatment of both early-stage and metastatic ErbB2-overexpressing (ErbB2+) breast cancer [235–238]. Subsequently, lapatinib, an orally bioavailable small molecule TKI dual targeting ErbB2 and EGFR, was also approved by FDA for the treatment of patients with advanced ErbB2+ breast cancer in combination with capecitabine [239]. Unfortunately, resistance to both trastuzumab and lapatinib has greatly limited the efficacy of ErbB2-targeted therapy [240]. Numerous mechanisms including loss of phosphatase and tensin homolog (PTEN) and activating mutations in genes coding for components of the PI3K/Akt/mTOR pathway have been proposed that may mediate de novo and acquired resistance to trastuzumab and lapatinib [241, 242]. Moreover,

our studies and others have demonstrated that increased activation of ErbB3 signaling plays a critical role in the resistance to ErbB2-targeted therapy in breast cancer [243–245]. These findings are further confirmed by a study indicating that ADAM10-mediated release of heregulin confers resistance to trastuzumab by activating ErbB3 [246]. Recently, to explore the influence of microenvironment signals on HER2-targeted TKI response, Watson et al. assessed the effects of >2500 different combinations of 56 soluble and 46 matrix microenvironmental proteins on outgrowth of lapatinib-treated HER2+ breast cancer cells using an emerging technology termed microenvironment microarrays (MEMA) [247]. It was demonstrated that NRG1β and hepatocyte growth factor (HGF) are the most significant factors to enhance outgrowth of HER2+ breast cancer cells in the presence of lapatinib. Specifically, NRG1β attenuated the response of the luminal-like HER2+ (L-HER2+) cells to lapatinib, whereas HGF attenuated the lapatinib sensitivity in the basal-like (HER2E) cells. This elegant work suggests that different mechanisms underlying resistance to HER2-TKI lapatinib may be due to the complexity of microenvironment as well as differences in signaling network wiring and architecture in different subtype cells. These findings reinforce the notion that tissue microenvironments are remarkably complex and intertwined in cancer biology [248].

1.3.3.3 Resistance to Other Therapy

Endocrine therapy such as tamoxifen, an antiestrogen agent, is commonly used in the treatment of patients with estrogen receptor-positive (ER+) breast cancer, a subtype accounting for about 80% of all breast cancers [249]. Although patients benefit a lot from tamoxifen treatment, resistance to this agent is a serious problem in clinic [250]. In the current body of knowledge, multiple mechanisms responsible for endocrine resistance have been proposed and include deregulation of various components of the ER pathway itself [251], alterations in cell cycle regulators such as MYC or cyclin D1, and the activation of alternative signaling pathways [252]. Among these, increased expression or aberrant activation of ErbB signaling has been extensively investigated and associated with both experimental and clinical endocrine therapy resistance [204, 253]. ER+ breast cancer patients with co-expression of ErbB2 and ErbB3 were significantly more likely to relapse on tamoxifen [254]. Direct evidence of the involvement of neuregulin/ErbB3 in tamoxifen resistance was provided by Liu et al. whose studies showed that downregulation of ErbB3 by a siRNA abrogated ErbB2-mediated tamoxifen resistance in breast cancer cells [55]. Furthermore, overexpression of HRG-β2 was reported to induce hormone-independent phenotype of ER+ breast cancer cells and resistant to tamoxifen via constitutive activation of ErbB signaling [89].

1.4 Role of Neuregulin Signaling in Regulation of Tumor Microenvironment

As an important part of immune infiltrates in TME, tumor-educated macrophages at the primary site promote tumor initiation and malignant progression via supporting tumor-associated angiogenesis; enhancing tumor cell invasion, migration, and intravasation; as well as suppression of antitumor immune responses [255, 256]. As earlier mentioned, a paracrine interaction involving reciprocal signaling between carcinoma cells and macrophages involving EGF and CSF-1 has been demonstrated to be required for tumor cell migration in mammary tumors [180, 257]. The finding that this EGF/CSF-1 paracrine invasion loop can be triggered by HRG-β1 [188], along with the fact that tumor cell-derived NRG-1 induces upregulation of JAG1 in macrophages [192], indicates that macrophages are subjected to a fine tune regulated by NRG signaling.

Nerves in the TME also play roles in tumor progression [258, 259]. It has been shown that, in addition to vascular and lymphatic systems, nerve system may serve as an alternative route for dissemination of cancer cells [260]. Cancer cells can grow around existing nerves and eventually invade them, in a process defined as perineural invasion (PNI) [261]. To date, PNI has

been observed in a variety of cancers, including pancreatic, prostate, colorectal, and others. PNI is generally associated with a poor prognosis and can cause severe pain in patients [262]. In a landmark publication, Magnon and colleagues provided experimental evidence showing that autonomic nerve sprouting in prostate tumors was essential for the progression of prostate cancers [263]. Later on, vagal innervation was demonstrated to contribute to gastric tumorigenesis via M3 receptor-mediated Wnt signaling in the stem cells [264]. Further investigation revealed that Dclk1+ tuft cells and nerves were the main sources of acetylcholine (ACh) within the gastric mucosa [265]. While cholinergic stimulation was evidenced to induce nerve growth factor (NGF) expression in the gastric epithelium, NGF/Trk signaling in turn was demonstrated to regulate mucosal innervation and promote carcinogenesis [265]. Considering the importance of NRG signaling in the development of nervous system [12, 266], these findings have shed a new light on the possible nerve-dependent mechanism of NRG signaling in regulating tumorigenesis [267].

Inducing angiogenesis is one of the key hallmarks of both primary and metastatic cancer [2]. When the primary tumor or metastases grow to a certain extent, oxygen and nutrient supply and the discharge of metabolic wastes and carbon dioxide are insufficient. Thus, the diameter of cancer can rarely exceed 2–3 mm without neovascularization. Hypoxia in TME is a key driver of transition from pre-vascular hyperplasia to highly vascularized and progressively outgrowing tumors termed "angiogenic switch," a process being fine-tuned by factors that either induce or inhibit angiogenesis [268, 269]. Among many reported pro-angiogenic proteins, vascular endothelial growth factor (VEGF) mainly secreted by cancer cells is now known to be central to this process [270]. Moreover, a large body of evidence indicates that angiogenic programming of tumor tissue is regulated by TME in concert with cancer cells [271]. Once the blood vessels grow into the tumor, the way of supplying nutrients and oxygen to the tumor tissue changes from peripheral diffusion to blood perfusion, and its metabolic wastes can be eliminated in time. In addition, tumor blood vessels can also determine the pathophysiology, growth, invasion, and metastasis of cancer, as well as its response to various treatments [272]. In normal condition, the neuregulin signaling has been demonstrated to play an important role in development of cardiovascular system [273, 274]. In a recent study, Nrg4 was also showed to be an angiogenic factor involved in maintaining adipose tissue vasculature [275]. Given the findings that the expression of pro-angiogenic proteins can be induced by several activated oncogenes including *ErbB2* [276, 277], the role of neuregulin signaling in the process of tumor angiogenesis has attracted much research interest as early as in the very beginning of this century. It was revealed by Yen et al. for the first time that HRG β1 can selectively upregulate the expression of VEGF in ErbB2-overexpressing breast cancer cells [278]. The induced expression of VEGF by HRG β1 was further confirmed by two independent research groups thereafter [279, 280]. Furthermore, HRG signaling-induced VEGF expression was also found in colon cancer [281].

Upon activation, normally quiescent vasculature sprouts new vessels to sustain the expanding growth of tumor. During this process, the recruitment of pericytes by platelet-derived growth factor-B (PDGFB) in TME was demonstrated to play an important role in maintaining appropriate vascular morphogenesis [282–284]. Pericytes vary not only in their morphology but also in protein markers they expressed as well as their origin [285]. Importantly, only type-2 pericytes were demonstrated to participate in normal and tumoral angiogenesis [286]. Taking into consideration the role of HIF signaling in regulating the secretion of PDGFB by endothelial cells [287], as well as the reported cross talk between HER2 and HIF signalings [288, 289], it is of great interest to explore the more exact role of NRG signaling in tumor angiogenesis.

1.5   Targeting of Neuregulin Signaling in Cancer Therapy

Given the pivotal oncogenic role of aberrant NRG signaling in a wide variety of human cancers, therapeutic targeting of NRG signaling in

cancer treatment has long been proposed and extensively studied. Strategies developed for NRG signaling-targeted therapy are different owing to the broad spectrum of casual mutations/aberrations unraveled. Some of them have been successfully approved for clinic application in cancer therapy and achieved favorable outcome. Since both EGFR- and ErbB2-targeted therapies have been extensively reviewed [290–292], our discussion mainly focuses on, but is not restricted to, NRG/ErbB3-targeted therapy in the following section.

Unlike its close relatives EGFR and ErbB2, less attention has been paid to the oncogenic functions of ErbB3 due to its weak kinase activity. However, during the last two decades, ErbB3 has been shown to be a direct therapeutic target in cancer treatment because of its role in tumor biology [293]. Currently, strategies developed for ErbB3-targeted therapy are mainly focused on blocking its activation through antibodies. The various ErbB3-targeted antibodies, including seribantumab (also known as MM-121/SAR256212) [294], LJM716 [295], and patritumab (or U3–1287) [296], have been demonstrated to inhibit ErbB3 pathway activation via different ways. MM-121, a fully humanized monoclonal antibody that interferes in binding of HRG to ErbB3, has been shown to effectively block ligand-dependent activation of ErbB3 induced by either EGFR, HER2, or MET [297]. In our own studies, we found that targeting of ErbB3 with MM-121 not only potentiated antitumor activity of paclitaxel against ErbB2+ breast cancer [298] but also had a potential of reversing trastuzumab resistance [299]. Recently, patritumab was evidenced to overcome ligand-mediated resistance to trastuzumab in ErbB2+ breast cancer via synergistically targeting of ErbB2/ ErbB3 signaling axis [300]. With the significant advances in antibody engineering technologies, strategies that simultaneously target multiple receptors with bispecific or multispecific antibodies have been developed and demonstrated to circumvent the limitations of conventional mono-specific therapies and achieved enhanced therapeutic efficacy [301]. MEHD7945A, a monoclonal antibody that dually targets EGFR and ErbB3 [302], has been shown to be more effective than a combination of cetuximab and anti-HER3 antibody at inhibiting both EGFR/HER3 signaling and tumor growth [303]. Although multiple phase I and II trials have been opened for various ErbB3-targeted antibodies [304, 305], clinical benefits of the antibodies as single agents have not been reported. In a randomized phase II trial of paclitaxel with or without seribantumab in patients with advanced platinum-resistant or platinum-refractory ovarian cancer, although no difference in progression-free survival (PFS) between the two arms was reported, the authors' exploratory analyses suggested that high HRG and low ErbB2 might be predictive of seribantumab benefit [306]. More recently, it was reported that the combination of SAR256212 and PI3K inhibitor SAR245408 for patients with metastatic or locally advanced solid tumors resulted in stable disease as the best response without effect on the pharmacokinetics of either drug, and the side effects seen in combination were similar to the profiles of each individual drug [307]. These results of clinical trials indicate that deliberate selection of patient and combinatory application with other treatments will be critical for the clinical practice of ErbB3-targeted therapy in the future [308].

In addition to blocking antibody, novel approaches targeting ErbB3 have also been proposed [309]. EZN-3920, a locked nucleic acid (LNA)-based ErbB3 antisense oligonucleotide, has been demonstrated to inhibit growth of xenograft models of breast and lung cancer cell lines via specific downregulation of ErbB3 [310]. As alterations in chromatin structure by histone modification and/or DNA methylation have been extensively correlated with cancer development, progression, and resistance to therapy [311, 312], epigenetic targeting is emerging as a promising therapeutic strategy for cancer treatment [313]. Histone deacetylases (HDACs), whose deregulation is evidenced to play an important role in aberrant gene expression in tumorigenesis, have long been recognized as druggable targets [314]. We previously reported that the class I HDAC inhibitor entinostat (also known as MS-275 or

SNDX-275) specifically enhanced expression of miR-125a, miR-125b, and miR-205, which acted in concert to downregulate ErbB2 and ErbB3 and selectively induced apoptosis in ErbB2-overexpressing breast cancer cells [315–317]. Recently, we found that valproic acid (VPA), a safely used anticonvulsant drug with reported HDACi capability, held an antitumor activity selectively against EGFR/ErbB2/ErbB3-coexpressing pancreatic cancer via induction of ErbB family members-targeting microRNAs [318]. Thus, miRNA-mediated epigenetic regulation may represent a new mechanism inactivating ErbB2/ErbB3 [319].

Since ligand binding is indispensable for successful eliciting of NRG/ErbB signaling, it is rational that specific downregulation of NRG and/or blocking its binding to ErbB3 should be an attractive strategy for interrupting this signaling. Actually, in the very beginning of this century, it was discovered that blockade of HRG expression using an antisense nucleotide technology resulted in inhibition of cell proliferation and anchorage-independent growth, as well as suppression of invasive potential of breast cancer cells in vitro [320]. Targeting of ADAM17, a major ErbB ligand sheddase, was also reported to inhibit ErbB3 and EGFR pathways through preventing the processing and activation of multiple ErbB ligands [38]. Neutralization antibodies have been extensively explored in targeting excess ligands in cancer therapeutics. By using two self-developed blocking antibodies of NRG1, Hegde et al. reported a successful inhibition of NRG1 signaling in NSCLC, leading to an enhanced duration of the response to chemotherapy [321]. Moreover, a NRG1-specific antibody 7E3 has been demonstrated as a promising antitumor agent against pancreatic cancer recently. 7E3 not only promotes antibody-dependent cellular cytotoxicity (ADCC) in NRG1-positive pancreatic cancer cells and cancer-associated fibroblasts (CAFs) and inhibits NRG1-associated signaling pathway induction in vitro; it also suppresses migration and growth of pancreatic cancer cells co-cultured with CAFs, both in vitro and in vivo using orthotopic pancreatic cancer xenografts [322]. Large body of functional studies has confirmed that miRNA dysregulation plays a causal role in many cases of cancer. Insights into the roles of miRNAs in cancer have made them attractive tools and targets for novel therapeutic approaches [323]. MiRNAs may act as tumor suppressors or oncogenes (oncomiRs), and miRNA mimics and molecules targeted at miRNAs (antimiRs) have shown promise in preclinical development. In a recent study, miR-296-5p was demonstrated to be significantly downregulated in HCC tissues, and introduced miR-296-5p was able to suppress EMT of HCC via direct targeting of NRG1 [169]. Thus, these findings have raised the possibility of miRNA therapeutics in NRG1-targeted therapy, which deserves further investigation. In addition, with the landmark finding of *CD74–NRG1* gene fusions in lung adenocarcinoma in 2014 [107], much effort has been made in exploring *NRG1* fusion-targeted therapy in cancer management [324]. Although strategies proposed for *NRG1* fusion-targeted therapy are still focused on interruption of downstream ErbB signaling [325–327], whether *NRG1* fusion itself may act as a direct druggable target is of great interest.

1.6 Conclusions and Future Perspectives

Although extensive effort has concentrated on elucidating the role of NRG signaling in the tumor microenvironment, several critical questions have been raised owing to the progress in some rapidly evolving fields of cancer research. Firstly, with the increasing recognition of link between the microbiota and cancer [328], the identification of intratumor microbiota has broadened the dimension of complexity of TME [329]. Microbiota has been demonstrated to play a key role in carcinogenesis and regulation of the response to therapy through a variety of mechanisms such as bacterial dysbiosis, production of genotoxins, pathobionts, and disruption of the host metabolism [330]. In a cross-sectional study, Tsay et al. reported that enrichment of the lower airway microbiota with oral commensals was associated with upregula-

tion of the PI3K signaling pathway in lung cancer [331]. Since the underlying mechanism of microbiota-induced upregulation of PI3K pathway remains undiscovered, whether NRG signaling is involved in this biological process deserves further exploration. Secondly, although anticancer immunotherapies involving the use of immune checkpoint inhibitors or adoptive cellular transfer have achieved promising clinical outcome, resistance to immunotherapy is still a major obstacle to be overcome [332, 333]. As has been revealed by two independent groups, loss of PTEN results in resistance to T-cell-mediated immunotherapy [334, 335]. These findings may hint a causal role of aberrant NRG signaling in resistance to immunotherapy. Thus, it will be of special interest to figure out whether simultaneous targeting of NRG signaling may enhance the efficacy of immunotherapy. Finally, exosome-mediated communication within TME has been recognized as an important player in regulating tumor progression [336]. An improved understanding of whether NRGs may be present in exosome and act locally and/or distantly on eliciting downstream signaling will be of great help in the guidance of developing novel NRG-targeted therapy, such as eliminating oncogenic exosomes with aptamer-functionalized nanoparticles [337]. In conclusion, we believe that the answer of these questions will offer a clearer understanding of the role of NRG signaling in the TME and point out the future direction of mechanism-based NRG signaling-targeted therapy.

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