Paracrine interactions among neoplastic and nonneoplastic cells in the immediate tumor microenvironment are important for tumor growth and metastatic spreading. Most of the studies in the past decade addressing these cellular interactions have focused on tumor cell-derived soluble molecules. Recently, these studies and interest have shifted to nanosized extracellular vesicles (EVs) and especially ectosome and exosome-associated molecules [1]. They contain not only proteins, but also lipids, mRNA, and microRNA [1], which can regulate gene expression in their target cells in a much more pleiotropic manner [1]. While exosomes originate by a sequential process of inward budding of late endosomes, producing multivesicular bodies (MVBs), followed by release of internal microvesicles into the microenvironment by fusion of the MVBs with the plasma membrane [1, 2], ectosomes bud from plasma membrane, particularly from plasma membrane protrusions (e.g., microvilli) [1]. However, difficulties in obtaining homogeneous exosomal and ectosomal preparations result in incomplete understanding of their formation, composition, and functions [3]. Trafficking of biological materials across cellular membranes is part of any normal cell homeostasis, to maintain proper compartmentalization of important molecules. The physiological functions of EVs are extremely diverse (e.g., cell-cell communication, cellular differentiation, immunity, and inflammation) [4–8]. However, in pathological states, such as cancer, aberrant activity of the export machinery results in expulsion of a number of key proteins and microRNA that modify the tumor microenvironment, in turn stimulating the release of EVs from stromal and immune-competent cells. In cancers, such vehicles might play a role in carcinogenesis and disease progression and promote formation of the premetastatic niche [9–11]. In the present special issue on transmission of information in neoplasia by extracellular vesicles, review articles and research paper illustrate the relevance of EVs to cancer growth and metastasis.

C. Soekmadji and C. C. Nelson discuss the current available literature about the role of EV-mediated drug resistance in cancers, with a particular focus on advanced prostate cancer. Presence of multidrug resistance proteins on the EV membrane, enrichment of ceramide, and sequestration of anticancer drugs are all potential EV-mediated mechanisms to limit the bioavailability or efficacy of anticancer agents.

T. M. Green et al. review the effects of EVs released by breast cancer cells through transfer of mRNA, microRNA, and proteins to different recipient cells within the tumor microenvironment, both in an autocrine and in a paracrine manner, which have a significant impact on signaling pathways, mRNA transcription, and protein expression. The authors point to proteins and microRNA identified within breast cancer-released EVs that give insight as to the nature and severity of the disease and could serve as possible diagnostic markers. Emphasis is also placed on multiple mechanisms by which breast cancer cells avoid immune system
recognition through EVs, such as secretion of immuno-
suppressive proteins, inhibition of NK cell proliferation, or
a decrease in T cell cytotoxicity. Finally, potential benefits
deriving from the use of EVs as a vehicle for delivery of anti-
breast cancer drugs are discussed.

T. Sun et al. point to exosome-derived noncoding RNA
and in particular microRNA as important molecules in lung
cancer biology, facilitating lung cancer growth and meta-
stasis. Both the EV field and the microRNA fields being in their
infancy, it is conceivable that many biological mechanisms
crucial for lung carcinogenesis and progression have yet to
be discovered.

Z. Qian et al. review the current literature in the field of
EV-mediated changes in the epigenetics of cancer microenvi-
ronment. Some of the proteins and nucleic acids transmitted
through EVs to recipient cells participate in DNA methyl-
ation, histone modification, and posttranscriptional regulation
of RNA. They may be responsible for altering expression of
oncogenes and tumor suppressor genes in recipient cells.

S. Raimondo et al. examine the role of EVs released from
cells of hematological malignancies during cancer progres-
sion, mainly focusing on the specific microenvironment of
hematological diseases, that is, the bone marrow. Blast cells
from acute myeloid leukemia and chronic myeloid leukemia
are able to initiate an exosome-mediated cell-cell commu-
nication with bone marrow stromal cells, thus affecting
angiogenesis and microenvironmental niche. Furthermore,
examples of the acquisition of EV-mediated chemotherapeu-
tic resistance are illustrated for multiple myeloma and B-cell
lymphoma.

In their review article, G. Schiera et al. summarize the
possible physiological roles of EVs in the nervous system,
where cell–cell communication is determinant in neuron
and glia differentiation as well as in the formation of the
blood-brain barrier. They further discuss the involvement
of EVs in the horizontal transfer of information for brain
pathologies such as Alzheimer’s disease, Parkinson’s disease,
and amyotrophic lateral sclerosis.

In the article entitled “High LIN28A Expressing Ovarian
Cancer Cells Secret Exosomes That Induce Invasion and
Migration in HEK293 Cells,” the authors present the results of
a study on IGROV1 ovarian cancer cells expressing high levels
of LIN28, a stem cell marker and emergent oncogenic driver.
Although LIN28 was not present in exosomes released by
cultures of IGROV1 cells, addition of exosomes to target cells
resulted in changes in expression of genes associated with
epithelial-mesenchymal transition and in a more aggressive
cell behavior.

Overall, the current issue of this journal highlights
the contribution of EVs to tumorigenesis and formation of
metastases and points to several potential strategies to
effectively utilize EVs for breast cancer diagnosis, prognosis,
and therapy.

References

[1] B. György, T. G. Szabó, M. Pásztoi et al., “Membrane vesicles,
current state-of-the-art: emerging role of extracellular vesicles,”
Cellular and Molecular Life Sciences, vol. 68, no. 16, pp. 2667–
2688, 2011.
tion, biogenesis and function,” Nature Reviews Immunology, vol.
2, no. 8, pp. 569–579, 2002.
ison of ultracentrifugation, density gradient separation, and
immunoaffinity capture methods for isolating human colon
cancer cell line LIM1863-derived exosomes,” Methods, vol. 56,
membrane sheath formation by oligodendrocyte-derived
exosome-like vesicles,” The Journal of Biological Chemistry,
protective messages during oxidative stress; possible role of
exosomal shuttle RNA,” PloS ONE, vol. 5, no. 12, Article ID
e15353, 2010.
Wieczorek, and M. Z. Ratajczak, “Membrane-derived micro-
vesicles: important and underappreciated mediators of cell-to-
cell communication,” Leukemia, vol. 20, no. 9, pp. 1487–1495,
2006.
[7] A. Janowska-Wieczorek, M. Majka, J. Kijowski et al., “Platelet-
derived microparticles bind to hematopoietic stem/progenitor
perform cell-independent microRNA biogenesis and promote
exosomes educate bone marrow progenitor cells toward a pro-
metastatic phenotype through MET,” Nature Medicine, vol. 18,
no. 6, pp. 883–891, 2012.
of local and distant intercellular communication that facilitates
the growth and metastasis of neoplastic lesions,” The American