The Eph receptor tyrosine kinases family and their membrane bound ligands, the ephrins, represents a complex signaling network of cell communication for cell sorting during tissue patterning in development and in the normal physiology and homeostasis of adult tissues. This molecular family has adapted to evolving tissue complexity in multicellular organisms through the emergence of more members and complex mechanisms of expression and signaling that result in the fine-tuning of cell positioning. Since their initial identification from an erythropoietin producing hepatocellular (Eph) carcinoma cell line in 1987, Eph/ephrin signaling has been a matter of intensive investigation for their plausible role in cancer. Similarly to their context-dependent modus operandi in normal tissues, Eph/ephrin signaling in cancer is an intricate and puzzling network of events that tumors “manage” to their benefit in multiple aspects like cell adhesion to substrate, migration, invasion or growth.

The collection of articles in this issue of Cell Adhesion & Migration, kindly contributed by leading experts in the field, addresses some of the new and exciting facets of Eph/ephrin signaling in cancer and other relevant aspects of this signaling system with implications in this disease.

An intriguingly aspect of this signaling system is the significance of co-expression at the single cell level which can affect the cell outcome. Receptor-ligand interactions in cis and the formation of heterocomplexes formed by various members, including kinase activity defective receptors like EphB6 or EphA10 and/or splice variants, can affect the overall signal strength and/or quality thus modulating the cellular response under control. Thus, identifying the Eph/ephrin-omic harbored by distinct cell types or in a context dependent way is a mandatory step to go forward in our knowledge of this system. A promising step toward this challenge is the pilot study here presented by Roberta Noberini, Elena Rubio de la Torre and Elena B. Pasquale, who took advantage of the ephrin binding promiscuities to develop an approach where binding to ephrin Fc fusion proteins immobilized on beads is used to isolate the repertoire of Eph receptors expressed in a biological sample and characterized through mass spectrometry. Besides, they report new binding promiscuities between recombinant Fc receptors and ligands not previously appreciated.

The manuscript from Birgit Mosch, Doreen Pietzsch and Jens Pietzsch reports changes in EphA2 and EphA3 expressions in several melanoma cell lines after X-irradiation, which could be related with their metastatic properties after treatment. Interestingly, they observed inverse effects between EphA2 and EphA3 expressions, suggesting that they could share regulatory mechanisms of expression. This prompts to the possible own regulation that could exist within the family, as pointed out by Dina N. Arvanitis and Alice Davy in this issue.

Adult stem cell function and their associated niches are under the regulation of Eph/ephrin signaling in several epithelial and non-epithelial compartments. The intestine is one example where EphB receptors regulate normal differentiation within the crypts and have dual roles in associated cancers, acting both as tumor promoters and suppressors at different stages of tumor progression. Maria Genander clearly depicts how epithelial stem cell niches can be maintained through Eph/ephrin signaling and discusses how epithelial tumors can escape from Eph/ephrin suppressor roles that maintain the homeostasis of the normal niche.

Eph/ephrins work through complementary or overlapping expression domains and the formation of gradients in many instances which points to the existence of tight regulatory mechanisms of spatial and temporal expression. One challenge therefore, has been to understand the transcriptional and post-transcriptional control of their expression. The review from Dina N. Arvanitis and Alice Davy nicely presents the most up-to-date data concerning to regulation of Eph/ephrin gene expression and its relationship with cancer biology. They further highlight that they could self regulate into their own highly precise and combinatorial expression patterns, as one of the several outcomes from Eph/ephrin bidirectional signaling. Some of these principles could underlay the observations made by B. Mosch et al. in the inverse regulation of EphA2 and EphA3 after X-radiation of melanomas, presented in this issue.

The review from Philip Kaenel, Mischa Mosimann and Anne-Catherine Andres highlights the importance of Eph/ephrin signaling in the homeostasis and development of the mammary gland and how this could be altered in the development of breast cancer. The mammary gland is a very nice model of plastic organ in the adult that continuously remodels throughout life and where misregulation of Eph/ephrin signaling could...
initiate and/or propagate cancer development. The epithelial unit of the mammary gland follows a developmental pattern of branching morphogenesis guided by Eph/ephrin signaling and later on in the adult in response to hormonal status. The authors highlight the tumor promoting and suppressor activities of Eph/ephrin in breast cancer in relation to their morphogenetic role in the gland.

Bone modeling and remodeling is largely dependent on Eph/ephrin signaling and alterations in this signaling system has been related to several bone associated diseases. Koichi Matsuo and Natsuko Otaki review our current knowledge in bone modeling and remodeling through Eph/ephrin signaling highlighting they role in bone diseases including cancer. They clearly depict how Eph/ephrin signaling is interconnected with other molecular signals relevant to bone biology and their role in osteoblast/osteoclast bidirectional communication.

Overall, this collection of articles highlights the paradox of Eph/ephrin signaling that can result in both tumor suppressing or promoting effects enforcing that a deeper understanding of this signaling system is mandatory before their potential applicability in the development of novel cancer treatments.

Finally, I would like to thank the leading experts in the field who kindly contributed to this overview of Eph/ephrin signaling in cancer and those who have peer-reviewed and contributed enriching comments. I also want to thank those colleagues who I contacted and disturbed and whose interest in contributing was unfortunately precluded by lack of time.

Many thanks for sharing your wisdom!

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