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EDITORIAL

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Cell movement is a fundamental process of normal cellular physiology and pathophysiology. Abnormal regulation of cell migration is a common denominator of many medical disorders, including cancer metastasis, autoimmune disease and inflammation. Increased interest in the targeting of cell migration and invasion, which has potential for therapeutic intervention in many diseases are behind this special themed issue. Thus, the focus of this issue is centred on the control of cellular cytoskeletal dynamics and cellular or tissue microenvironment sensors. Novel therapeutic opportunities targeting regulation of cell migration are discussed including the emerging roles of tetraspanins, phosphoinositides, transient receptor potential cation channels, stromal interaction molecules and calcium release-activated calcium modulators. Better understanding of these regulatory factors will hopefully bring greater attention to strategically targeting aberrant cell migration, which has many therapeutic implications for common human diseases.

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The regulation of cell migration is complex and involves sequential chains of events in both normal and pathological conditions. This complexity has proven to be a challenge in therapeutic development but at the same time offers interventional opportunities. Cytoskeletal dynamics involves various regulatory processes, which offers several potential intervention points for anti-migration drugs. In this issue, leading scientists in the area of inflammation, wound healing and tumour biology have contributed an overview of cell migration and perspectives on the clinical application of anti-migration therapeutics. There is discussion of new and/or emerging roles of novel therapeutic interventions targeting cytoskeletal dynamics such as membrane lipids, the Ras superfamily of small GTPase proteins, transmembrane spanning tetraspanins, calcium sensors and ion channels.

In cancer, cell migration is required for local invasion, angiogenesis and metastasis, which are common characteristics for all cancers, as reviewed by Hanahan and Weinberg 2011. Cancer morbidity and mortality are largely related to the spread of the primary, localized tumour to adjacent and distant sites. Appropriate management and treatment decisions for metastatic disease are crucial and are better informed by greater understanding of the metastatic process. There are common events that occur during metastasis: dissociation from the primary tumour mass, reorganization/remodelling of extracellular matrix, cell migration, recognition and traversal of endothelial cells into the vascular circulation and lodgement and proliferation within ectopic stroma. One of the key and initial events is the increased capability of cancer cells to move through tissue planes and escaping normal physiological constraints. The first of the anti-migration class of inhibitors to be approved for multiple sclerosis and Crohn's disease is natalizumab (Selewski *et al.*, 2010); the migration-inhibitory mode of action of natalizumab is through its antibody-tail binding to α4 integrin on lymphocytes preventing its binding to endothelial cells, hence transmigration across vascular endothelium (Yednock *et al.*, 1992; Tubridy *et al.*, 1999). Detchokul *et al.* (2014) have also reviewed the emerging role of members of the transmembrane-4-superfamily (or tetraspanins) in the regulation of cancer migratory processes and the potential of therapeutic targets against tetraspanins and their binding partners, including integrins, matrix metalloproteinases, EWI proteins (a cell surface immunoglobulin SF protein) and E-cadherin.

The cellular cytoskeleton is at the heart of the cell migration process in both normal and pathological conditions (Fletcher and Mullins, 2010; Stricker *et al.*, 2010; Rottner and Stradal, 2011; Ratheesh and Yap, 2012). An active change in cancer cytoskeletal dynamics results in manipulation of plasma membrane and cellular balance between cellular adhesion and motility which in turn determines cancer cell

movement. In this issue, Fife *et al*. (2014) discuss the role of the cytoskeletal proteins, namely actins, intermediate filaments and microtubules, in cancer migration and metastasis. In particular, the role of microtubules in the regulation of migration, invasion and metastasis in various cancers was highlighted. Increasing evidence reveal that microtubule and actin cytoskeletal dynamics are both controlled by Rho family of GTPases (Rho-GTPases). Microtubules, in turn, are able to mediate Rho-GTPases. Crosstalk between actin and microtubules does occur, which furthermore underscores the regulatory role of microtubule systems to the actin cytoskeletal regulation. This new knowledge opens doors to discovery of new biomarkers and therapeutic targets for cancer migration and metastasis. Biro *et al*. (2014) have also given a comprehensive review on the regulatory pathways of actomyosin dynamics in immune cell migration. They draw attention to the therapeutic intervention points from the downstream signalling in Rho-GTPase pathways such as Rho kinase (ROCK), Cdc42 and Rac. Increasing understanding of the control of these molecules has led to the development of pharmaceutical compounds acting against these molecules.

Another regulatory mechanism of the actin cytoskeleton dynamics is via actin binding proteins and membrane lipids, as reviewed by Wu *et al*. (2014). The PI3K signalling pathway (i.e. PI3K–AKT–mTOR) is well-recognized as dysregulated in many cancers, including breast cancer, multiple myeloma, leukaemia, lymphoma (Samuels and Waldman, 2010; Jensen *et al*., 2012) and inflammatory respiratory diseases (Ito *et al*., 2007; Doukas *et al*., 2009). Many candidate inhibitors have been developed to counteract members of this pathway (Liu *et al*., 2009; Cheng *et al*., 2013; Marcias-Perez and Flinn, 2013; Yang *et al*., 2013). Nevertheless, most single-agent cancer trials did not yield anticipated results (Fruman and Rommel, 2014), leading to further searches for more specific targeting such as different isoforms of PI3K (Ameriks and Venable, 2009). Chen *et al*., in this issue, has reviewed the current understanding of metabolism of phosphoinositides in particular $PI(4,5)P_2$ and $PI(3,4,5)P_2$, and discussed their multiple involvements in the regulation of actin binding proteins. These multidimensional roles of phosphoinositides may be indicative of challenging outcomes for targeting the PI3K signalling pathway, as seen in early phase clinical trials.

Earlier this year, the BJP published a very informative themed issue on transient receptor potential (TRP) channel superfamily (Holzer and Izzo, 2014) bringing forth their importance in many pathological conditions, namely pain sensation, bladder dysfunction and pulmonary diseases. In the current issue, Nielsen *et al*. (2014) comprehensively review the role of TRP channels and functional partners Ca^{2+} sensitive stromal interaction molecule (STIM)/calcium release-activated calcium modulator (ORAI) proteins in cancer migration and metastasis. Increasing evidence has been found of the role stromal cells play in cancer metastasis; TRP channels and STIM/ORAI proteins have a potential role in the regulation of crosstalk between cancer and stromal cells and thereby influence the migration of both cell types. Besides being cellular environmental sensors, TRP channels are linked to the actomyosin cytoskeleton. This review summarizes their role as sensors and effectors in cancer migration and metastasis and detailed subtype expression in various cancers was also summarized, supporting a potential role of these proteins as drug targets.

Taken together, these reviews represent for the reader a sample of active research in the cell migration field, the hope being that greater mechanistic understanding might now lead to novel therapeutic approaches to common conditions such as cancer and inflammatory disorders.

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