Asian Journal of Andrology (2011) 13, 177–178

www.nature.com/aja

RESEARCH HIGHLIGHT

Cancer cell migration: when red light switched to green

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Asian Journal of Andrology (2011) **13,** 177–178; doi:10.1038/aja.2010.176; published online 17 January 2011

The doctrine of 'the golden mean' of the Confucian certainly applies at the molecular level to cell growth and migration. It is critically important for tissue architecture and homeostasis that cells stop proliferation when reaching appropriate density and halt migration in a direction to avoid collision with others. This 'red light' to hinder cell movement is essential for maintaining contact inhibition of locomotion (CIL)—a phenomenon that a cell ceases to continue moving in the same direction when it comes into contact with another cell. The concept of CIL emerged initially from the early work of Abercrombie and Heaysman in the 1950s.[1] Deficiencies in this cell communication system may lead to uncontrolled cell migration towards neighboring cells—an invasive process often observed in cancer. Indeed, metastatic cancer cells have often gained the capability to migrate specifically towards non-malignant cells and away from its cancerous peers. Understanding the molecular basis of this selective migration will greatly enhance our ability to prevent cancer dissemination, a lethal process in a majority of tumor types. In a recent issue of *Nature Cell Biology*, Astin and colleagues[2] report that defective CIL between normal and cancerous cells is dictated by a switch of the repulsive 'red light'—the EphA receptor signaling—to the attractive 'green light', the EphB receptor signaling (Figure 1). These intriguing findings shed some light on the control of CIL and pave the way for future characterization of its role in cancer.

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It was hypothesized over four decades ago that the loss of contact inhibition of cell division and movement may form the biological basis of cancer.[3] The study of CIL, however, has been largely limited to neural crest cells.[4] This is, at least in part, due to the lack of molecular understanding of CIL and the difficulty in studying CIL *in vivo*. In the last decade, important advances have been made in the field of cell migration with the discovery of essential molecules involved in cell–cell contact such as ephrins and cadherins.[5] Excitement over CIL has thus re-emerged with a focus on its molecular basis and functions in diseases such as cancer.[6,7] In this study, Astin *et al.* attempted to understand CIL in prostate cancer cells and to determine its role in cancer metastasis using human prostate cell lines including non-tumorigenic primary prostate epithelial cells, and the tumorigenic DU145 and PC3 prostate cancer cells. They showed that all three cell types demonstrated normal homotypic CIL. However, unlike DU145 and prostate epithelial cells, PC3, the only one out of the three that are able to form distant metastases when injected subcutaneously in mice, failed to show heterotypic CIL. Instead of halting, PC3 cells continue their migration after contact with non-malignant cells such as fibroblasts and endothelial cells. This defective heterotypic CIL may work in concert with the normal homotypic CIL between PC3 cells to allow them to invade specifically towards non-malignant cells.

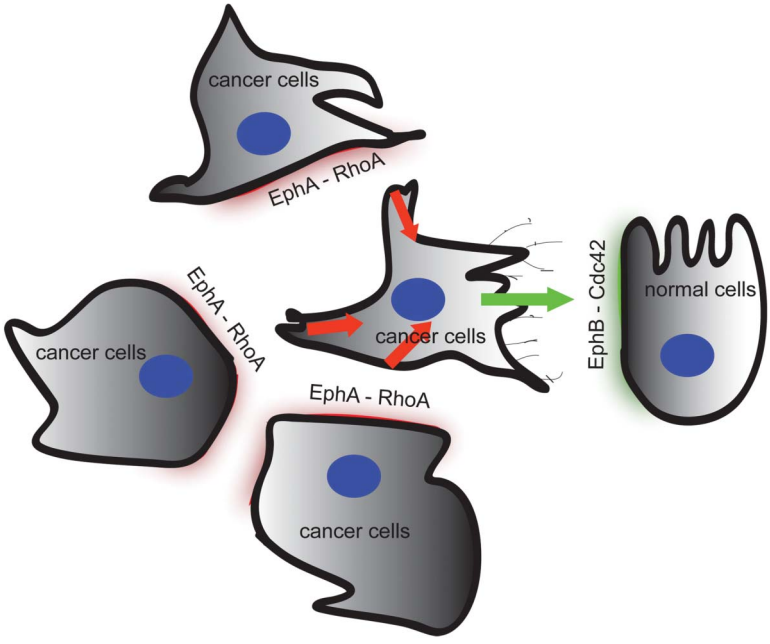

Figure 1 Cancer cell migration is controlled by competition amongst categories A and B Eph receptors. Normal homotypic CIL mediated by EphA–RhoA pathway—the 'red light'—ensures that cancer cells retract (red arrow) to avoid collision with its peers. However, a 'green light' is turned on *via* EphB–Cdc42 signaling when invasive cancer cells, such as PC3, come into contact with non-malignant cells. This 'green light' surpasses the 'red light', thus allowing cancer cells to invade (green arrow) specifically towards non-cancerous cells. CIL, contact inhibition of locomotion.

The authors next sought to determine why PC3 cells respond differentially when in contact with normal and cancerous cells. Although the molecular mechanisms that control CIL are largely unknown, it is perceived that efficient CIL will require a cell to first sense cell–cell contact and then transduce the signal inward. The molecules involved are thus most likely transmembrane proteins located on the cell surface. Astin *et al.* reasoned that Eph receptors are probable candidates for CIL response. Eph receptors are transmembrane tyrosine kinase receptors that bind specific ephrins, which are membrane-anchored proteins. There are two subclasses, A and B, of ephrins that preferentially interact with EphA and EphB receptors, respectively. Upon cell-to-cell contact, Eph receptors on one cell are engaged with ephrins anchored on the other, inducing intracellular signaling in both cells through Rho GTPases, which are a group of proteins that are key regulators of cytoskeletal reorganization. EphA/ephrin-A binding activates Rho GTPases such as RhoA for repulsive cell movement, while EphB/ephrin-B binding induces another set of Rho GTPases, Rac1 and Cdc42, to attract migration of both cells.[7,8] To understand the mechanisms of CIL in prostate cancer cells, Astin and colleagues first show that EphA receptors are expressed in all of the three cell lines and incubation with ephrin-A is sufficient to activate RhoA, resulting in cell retraction. Knockdown of EphA receptors abolished ephrin-A binding, thus leading to the loss of homotypic CIL between cancer cells. Therefore, all three cell lines possess normal EphA/ephrin-A signaling, excluding the involvement of this pathway in defective heterotypic CIL specific to PC3 cells.

By contrast, ephrin-B binds only to the surface of PC3 cells, which express markedly higher levels of EphBs than the other cells. Incubating PC3, but not DU145, cells with ephrin-B2 activates Cdc42 and induces the formation of filopodia. This suggests that EphBs on PC3 cell surface may be activated by ephrin-Bs expressed by contacting cells leading to the induction of filopodia and cell migration, i.e., the loss of CIL. Indeed, fibroblasts and endothelial cells express much higher levels of ephrin-Bs, but not ephrin-As, than PC3 cells. Importantly, knockdown of two EphB receptors, EphB4 and EphB3, in PC3 cells, abolished the induction of filopodia and restored CIL between PC3 and non-malignant cells. Analogous to this, PC3 cells overexpressing ectopic ephrin-Bs lost homotypic CIL.

Taken together, all three cell types exhibit normal homotypic CIL mediated by repulsive ephrin-A/EphA signaling—the 'red light'. However, due to its high level of EphBs, only PC3 cells, when come into contact with cells expressing ephrin-Bs—be it non-malignant fibroblasts or endothelial cells or ephrin-B-expressing PC3 cells, turn on the 'green light' *via* EphB/ephrin-Bs signaling. This 'green light' surpasses the 'red light', thus resulting in cell–cell attraction and defective CIL (Figure 1).

Cancer cells acquire a number of features, such as loss of CIL, to escape normal regulation by the human body. Loss of CIL facilitates cancer cell invasion of nearby tissues and establishment of distant metastasis. Strategies to restore CIL and prevent cancer cell invasion and metastasis will rely on comprehensive understanding of the complex molecular basis controlling CIL. The present report promises one such strategy. Although this study was limited to three prostate cell lines and was complicated by the various ephrins as well as Eph receptors, the findings warrant corroboration in other cancer cell types.

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