Summary. The ability of a cell to invade its surroundings is an important hallmark of malignant tumors and results from aberrant cell signaling mechanisms. The signal transduction that leads to tumor invasion can be broken down into major pathways. Even though the pathway systems are distinct in themselves, none of these pathways operate independently when it comes to transmitting signals that culminate in an invasive phenotype. That is, the malignant change in one receptor not only leads to malignant changes directly downstream but can also affect the molecules of many other pathways. Three major pathway systems involved in tumor invasion are discussed in this review: the integrin system, the insulin-like growth factor system, and the Rho family GTPases. Here we see that although the individual signaling systems can each contribute to invasion, each system is networked to others and should not be considered isolated. Each system is first reviewed as independent contributors to an invasive phenotype and then discussed in the context of interacting pathways that collectively result in tumor invasion.

Key words: Tumor invasion, Integrin, IGFPB, Rho, Crosstalk

Introduction

The most malignant characteristic of all cancers is their ability to grow beyond the confines of their original location. While some tumors (e.g., glioblastoma multiforme) are known for being locally invasive and remaining within the organ system and other tumors (e.g., pancreatic carcinoma) are known for metastasizing to distant sites, the spreading of cells in an uncontrolled manner is common to all cancers. Although this process can seem chaotic when observed from the phenotype perspective, a structured organization of the cell signals can be seen at the molecular level. Intracellular signaling comprises a complex and highly regulated network of pathways that are necessary for cell growth, replication, death, and survival. Players in this organized maze of pathways include ligands, receptors, kinases, adapter molecules, transcription factors, and other molecules, many with multiple roles and functions. Some molecules function strictly as agonists or antagonists, while others have dual roles in maintaining homeostasis, depending on the state of the cell. Perhaps the biggest challenge in signal transduction research is discerning the pathways that have gone awry, thereby causing cells to adopt a malignant and invasive phenotype—in other words, to become cancerous. Understanding and delineating the pathways involved in this process is particularly important because it provides us with the information needed in the pursuit of new therapy and improvements in current anticancer treatments. Today, some of the most active areas of research regarding cell invasion (to be covered in this article) include integrins, insulin-like growth factor (IGF) signaling, small GTPases, and the crosstalk between different pathways.

Integrins

Integrins are transmembrane receptors composed of an alpha and a beta subunit that are non-covalently linked. Together, the heterodimers form a receptor on the cell surface, with intracellular and extracellular domains responsible for controlling interactions of the cell with the extracellular matrix (ECM). Currently, at least 22 different integrin heterodimers have been identified (Hemler, 1999). Depending on the heterodimer composition, an integrin receptor shows high specificity for certain ECM ligands, including vitronectin, fibronectin, laminin, and collagen. In normal cells, integrins play key roles in the regulation of cell migration and attachment. These receptors also have the capacity to communicate intracellular signals that promote cell migration and survival. Defects in immune system response, specifically, defects related to cell movement (leukocyte trafficking), have been observed in mouse models lacking certain integrin function. For example, blockade or inhibition of integrin attenuates the immune response in autoimmune and inflammatory...
Tumor invasion signalling

In mice (Kudlacz et al., 2002; James et al., 2003). Further, the changes in the immune response have to do with the integrin’s ability to regulate leukocyte migration (Rose et al., 2001).

Integrins have been found to play an important role in tumor invasion in a wide variety of cancers. In hepatocarcinoma, inhibition of the integrins α1, α2, and β1 significantly inhibited growth factor–stimulated cell migration (Yang et al., 2003). In breast carcinomas, expression of the α6β4 integrin appeared to enhance tumor cell invasiveness (Chung et al., 2002). In metastatic prostate carcinoma, inhibition of the αvβ3 integrin correlated with an increase in cell migration (Chung et al., 2002). Conversely, in prostate carcinoma, expression of the αvβ3 integrin correlated with an increase in cell migration (Zheng et al., 1999; Manes et al., 2003). In ovarian carcinoma, increased expression of the αvβ1 integrin appeared to correlate with malignant effusions (Davidson et al., 2003). Therefore, these observations collectively show, the functional blocking of certain integrins (e.g., via antibody antagonists) is a potential therapeutic strategy for these types of cancers.

This inactivation of an integrin and consequential decrease in cell migration and invasion would likely require the blocking of at least one of two mechanisms. First, because cell migration depends on the cell’s ability to make contact with the cell’s substratum and integrins control cell attachment to the ECM, it is clear that it would be necessary to prevent the integrin from attaching to the ECM. Second, because integrin receptors themselves do not have any inherent enzymatic properties and only participate in signal transduction downstream from the receptor, it would be necessary to block the pathways downstream from an activated integrin receptor, which appear to promote pro-invasive phenotypes. An example of such an integrin is the activated high-affinity integrin that is recruited to the leading edge of lamellipodia in migrating endothelial cells (Kiosses et al., 2001). We would, however, have to determine which of these two mechanisms is involved in a particular integrin’s ability to contribute to cell invasion.

There is also evidence that alternatively spliced forms of integrin receptors play a role in cell invasion. These receptors have already been shown to alter normal cell migration and malignant cell proliferation. However, the expression of these alternatively spliced forms of integrins has only been found to decrease the movement of cells rather than promoting an invasive phenotype in human cell lines (Fornaro et al., 1998; Gimond et al., 2000). Nonetheless, in mice, an α6 splice variant has been linked to malignant conversion and the invasion of skin tumor cells (Tennenbaum et al., 1995). This thus shows that there are further aspects of integrin signaling that need to be understood. For example, perhaps splice variants maintain the same extracellular ligand contact but alter the intracellular signaling such that a cell becomes more invasive. Environmental conditions may also cause a particular splice variant to be dominant, thereby making a cell more invasive in certain environments. Integrins have further been shown to interact with the IGF system, which is discussed in greater detail in the next section. Indeed, interaction with this system has recently been found to play an important role in determining both normal cell migration during embryo development (Kabir-Salmani et al., 2004), malignant tumor growth, and the migration of breast cancer cells and multiple myeloma cells (Tai et al., 2003; Pereira et al., 2004). Because the IGF axis is an important modulator of cell growth, the coupling of integrin receptor pathways to this axis adds yet another dimension to an already complex signal transduction network that can produce both normal and aberrant cell proliferation. In addition, much remains to be elucidated regarding the crosstalk between integrins and the IGF system, the topic of the last section of this review.

Targeting integrin activity as a potential therapy for cancer is currently under much investigation. The most common approach to blocking integrin activity thus far is to neutralize the integrin receptor via antibodies. This method has already been shown to dramatically reduce cell migration in glioma cells (Tynnes et al., 1996; Haugland et al., 1997). However, recent advances in molecular biology, in particular RNA interference (RNAi) techniques, offer promise as ways to alter gene expression. Already, small interfering RNAs (siRNAs) have been recognized as a potential means of decreasing breast carcinoma invasion. For example, like the antibody inhibition of α6β4 integrin function, the genetic silencing of α6β4 integrin expression in breast carcinoma by siRNA successfully reduced cell invasion and migration (Lipscomb et al., 2003). Further in vivo experiments testing siRNA techniques are currently under way, and the findings will determine whether they have any potential application to cancer treatment.

A peptidomimetic agent synthesized to inhibit αvβ3/αvβ5 integrins also appears to be promising. The antagonist, S247, proved to be an effective inhibitor of colon cancer cell migration and invasion in vitro and in vivo. S247 appears to inhibit colon cancer cell invasion by inhibiting tumor angiogenesis and not by inhibiting the various direct downstream targets (e.g., Akt) (Reimnuth et al., 2003). Clearly, when targeting integrin receptors as a therapy for cancer, attention must be given to potential mechanisms other than the intracellular signals conveyed by the integrin receptor. Because some integrins interact with the RGD tripeptide sequence present in many ECM proteins, this interaction has been exploited as a potential target of therapy through the use of soluble RGD-peptides (Pierschbacher et al., 1987; Chen et al., 1997). Snake venom represents yet another approach to blocking integrins. In particular, lebectin, a C-type lectin contained in Macroviapera lebetina venom, has been shown to inhibit the integrin-mediated attachment and invasion of human tumor cells (Sarray et al., 2004). The snake venom disintegrin contortrostatin has been found to inhibit human glioma cell invasion by interfering with vitronectin/fibronectin adhesion.
Because a disintegrin interferes with an integrin receptor’s ability to bind to its ECM ligand, the use of disintegrin to prevent tumor spread is currently being examined. Although the disintegrin activity in snake venom has long been known, the study and development of anticancer agents with such a property has only just begun. Such anticancer therapy holds promise.

**Insulin-like growth factor (IGF) System**

In recent years, high circulating levels of the peptide hormone IGF-I have been linked to an increased risk of cancer. Currently, this is becoming an increasingly investigated area of cancer research since the positive correlation of IGF-I with cancer seemed to be found throughout various cancer types (Chan et al., 1998; Hankinson et al., 1998; Ma et al., 1999; Yu et al., 1999). Yet more mechanistic explanations of the IGF and its link to cancer remain to be discovered in just about all cancer types.

The IGF system includes a family of two growth factors (IGF-I, IGF-II), two receptors (IGF-IR, IGF-IIR), and multiple binding proteins (IGFBP 1-6). The bioavailability of IGF is regulated by its binding with IGFBPs, with IGFBP-3 being the most abundant circulating IGFBP. Most of the physiological effects from IGF occur through the IGF-IR at the cell surface. However, because IGF has a greater affinity for IGFBPs than for IGF-IR, IGFBPs are known to compete with IGF-IR activated downstream signaling. IGF-I is necessary for cells to enter the G1 phase, where a new round of cell division begins. Therefore, although at first it appears the binding of an IGFBP to IGF should be growth inhibitory (clearly sequestering IGF-I from IGF-IR), there is data showing that IGFBPs may also stimulate DNA synthesis by facilitating IGF binding to its receptor (Novosyadlyy et al., 2004) and therefore potentially stimulating cell growth and division. IGF-I-stimulated receptor is linked to the downstream activation of Akt, which phosphorylates (thereby inactivating) caspase 9 (Carpenter et al., 1993; Butler et al., 1998; Brunet et al., 1999; Zheng et al., 2000). The activation of Akt also culminates in the activation of NFκB, which stimulates the transcription of pro-survival genes (e.g., bcl-2) (Khwaja, 1999; Catz and Johnson 2001; Viatour et al., 2003). Both of these examples of the downstream effects of IGF-IR signaling show how IGF-I can promote cell survival and therefore underlie the importance of IGFBPs in regulating the amount of IGF-I at the cellular level. However, the regulatory processes that dictate whether IGFBPs are to either inhibit or enhance IGF pathways are very poorly understood and often confusing at present.

IGF-I also induces the expression of matrix metalloproteinases (MMPs) that participate in the breakdown of the basement membrane and remodeling of the ECM prior to invasion. In particular, IGF-I induces the expression of MMP-2, MT1-MMP, and MMP-9 (Long et al., 1998; Bredin et al., 2003; Zhang and Brodt, 2003). MMP-2 and MMP-9 are gelatinases that can cleave type IV collagen and gelatin. Through the IGF system, MMP-9 mediates the increased invasion of cells stimulated by IGF-I (Mira et al., 1999). MMP-7 affects circulating IGF-I levels by cleaving IGFBP-3 (the key regulator of free IGF-I levels), thereby increasing IGF-I signaling at the IGF-IR (Miyamoto et al., 2004). Further, the blocking of IGF-IR up-regulates IGFBP-3 in prostate cancer cells (Grzmil et al., 2004). Therefore, it is very likely that MMP-7 is also controlled (at least in part) by IGF-IR-stimulated downstream signaling, which in turn frees up more IGF-I because of its degradation of IGFBP-3. MMP-7 is also a unique MMP, in that it is only synthesized in cancer cells (Miyazaki et al., 1990; Nagashima et al., 1997). A positive feedback loop involving MMP-7 seems to explain how MMP-7 contributes to the continuous IGF-I stimulation of cell growth and invasion (Fig. 1).

IGF-II has the same structural homology as IGF-I. However, IGF-II can be bound by the insulin receptor A (IR-A) isoform in addition to the IGF-IR. IGF-II is overexpressed in malignant tumors and not in benign or normal adrenal tissue (Boullé et al., 1998), but little is known regarding whether IGF-II is linked to any pathways that trigger tumor invasion.

The IGF-IR has become a recent focus in studies of the IGF-axis in cancer because its involvement in cancer progression goes beyond the mere transduction of oncogenic signals downstream of the receptor that result in invasion. In particular, together with IGF-IR...
downstream signaling, IGF-IR also promotes a more invasive phenotype (Boullé et al., 1998; Brodt et al., 2001). One example is the overexpression of vascular endothelial growth factor C (VEGF-C), which is a known promoter of lymphatic metastasis in breast carcinoma that was recently found to be the result of a functional IGF-IR kinase domain (Tang et al., 2003). Once again, not only does a fully functional IGF-IR result in transduction of signals resulting in invasion, but it also triggers phenotype changes that, together in cooperation with IGF-IR downstream signaling, promote tumor spread. This therefore shows that merely studying the pathways downstream from IGF-IR may not give us a complete picture of the role of this receptor.

Consistent with the role of IGF-IR in the initiation of downstream signaling, the down-regulation of IGF-IR in a number of cancers has been shown to reduce cell proliferation and tumor dissemination (Boullé et al., 1998; Min et al., 2003; Zhao et al., 2004). For example, in a prognostic study done in patients with clear-cell renal carcinoma, the presence of IGF-IR was correlated with decreased patient survival (Parker et al., 2003), renal carcinoma, the presence of IGF-IR was correlated in a prognostic study done in patients with clear-cell renal carcinoma, the presence of IGF-IR was correlated with decreased patient survival. IGF-IR also promotes a more invasive phenotype (Boullé et al., 1998; Brodt et al., 2001). One example is the overexpression of vascular endothelial growth factor C (VEGF-C), which is a known promoter of lymphatic metastasis in breast carcinoma that was recently found to be the result of a functional IGF-IR kinase domain (Tang et al., 2003). Once again, not only does a fully functional IGF-IR result in transduction of signals resulting in invasion, but it also triggers phenotype changes that, together in cooperation with IGF-IR downstream signaling, promote tumor spread. This therefore shows that merely studying the pathways downstream from IGF-IR may not give us a complete picture of the role of this receptor.

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two most investigated groups of proteins are the Rho-like proteins and the Rac-like proteins.

The Rho-like subfamily of proteins in general contributes to the formation of stress fibers and focal adhesions in cells. RhoC, in particular, appears to play a significant role in the promotion of tumor invasion (Clark et al., 2000). For example, the direct overexpression of RhoC and the constitutive expression of an active mutant of RhoC were both observed to up-regulate the expression of invasion-enhancing genes in breast carcinoma cells (Wu et al., 2004). Further, the use of drug inhibitors that altered RhoC subcellular localization inhibited in vitro and in vivo spread of melanoma cells (Collisson et al., 2003). Much remains to be elucidated regarding the mechanism of RhoC’s regulation of invasion. Currently, all we know is that some downstream genes are up-regulated and that this results in certain phenotypes. It is unclear which downstream genes are at the next step in the RhoC cascade leading to cell invasion. The interaction of RhoC with other small GTPases (such as the growth-inhibiting RhoB) may potentially show a balance between members of this important class of proteins.

The Rac-like subfamily appears to induce membrane ruffling and the generation of lamellipodia (i.e., protrusions from the leading edge of migrating cells), which is important for cell motility (Ridley et al., 1992). The Rac proteins are also known to stimulate growth transformation, activate Jun N-terminal kinase (JNK), and promote cell survival. Rac has even been shown to directly promote the invasion of fibrosarcoma cells by activating MMP-2 in the degradation of a collagen barrier (Zhuge and Xu, 2001). However, in renal cell carcinoma, there is evidence that Rac signaling inhibits invasion by up-regulating inhibitors of MMPs (Engers et al., 2001). And, once again, we cannot rule out the existence of a negative feedback loop that attenuates the effects of an up-regulated protein such as Rac (Fig. 2).

The upstream activator of Rac, known as T-lymphoma invasion and metastasis (Tiam1), has recently received much attention in studies of Rac activity. Although Tiam1 deficiency in mice resulted in the formation of fewer Ras-induced tumors, a greater proportion of these tumors were able to convert to a malignant phenotype (Malliri et al., 2002). Here again we see the dual effects that a single protein (a gene expression regulator in this case) can have on the resulting tumor phenotype. This paradox of a decreased tumor cell number coupled with increased cell malignancy is a trend that is being observed more and more in cancer research. Therefore, targeting a protein such as Tiam1 remains a possible therapeutic strategy, yet the effects on tumor growth currently remain unclear.

Furthermore, it has been found that tumors are able to switch between different modes of invasion by using separate Rho signaling pathways (Sahai and Marshall, 2003). Indeed, it appears that some tumor cells employ multiple Rho signaling pathways that trigger the cell’s invasiveness and that the cell can switch between pathways, potentially limiting the effectiveness of certain anti-cancer agents. This underlines the importance of finding a synergistic therapy that can block multiple pathways and hence completely abolish metastasis. Indeed, perhaps some of the most devastating cancers today are able to bypass current therapies simply because they can make use of multiple signaling pathways that all result in invasion. Therefore, in the search for better therapies, rather than looking for stronger inhibitors of a single pathway, the first step may be to delineate the other pathways involved that are also contributing to the same phenotype.

**Pathway crosstalk**

Intersecting pathways play a major role in the resulting phenotype in any signal transduction. However, currently, little is known about how pathway crosstalk leads to tumor invasion. Nonetheless, there is evidence that some phenotypes are the result of more than just the cascading events of one pathway. Indeed, the direct interaction of members of one pathway with a member of another pathway has been observed, and the resulting phenotype can either be different from the activation of one of the pathways alone or be amplified in almost a synergistic manner. In addition, as already noted, signaling pathways that contribute to tumor progression are not always strictly isolated to any one system. For example, as discussed earlier, tumor growth and invasion can be affected by the interaction of integrins with the IGF system. In particular, the IGFBPs appear to mediate...
Much of the crosstalk between the IGF axis with other pathways, most likely as a result of the IGF-independent functions of the IGFBPs. Interestingly, however, although IGFBP-2 upregulates invasion-enhancing genes (Wang et al., 2003), the interaction of IGFBP-2 with overexpressed αvβ3 integrin appears to reduce tumor growth and migration in breast cancer cells (Pereira et al., 2004). This shows that the role of a protein can become distinctly opposite when the protein is bound to a molecule from another pathway. IGFBP-3 has been hypothesized to be linked to the EGF system, resulting in growth proliferation (Butt et al., 2004). This could establish a link between the IGF and EGF system, which would be an important link because the EGF system is a major crossroad of tumor invasion signal transduction, which will be discussed further below.

There are also data showing links between the IGFBPs with other pathways. For example, the previous finding that IGFBP-1 binds to the α5β1 integrin (in an RGD-dependent manner) and thereby stimulates cell migration (Jones et al., 1993). The fact that IGFBP-2 also contains an RGD motif suggested that IGFBP2 may also bind integrin thus affect cellular adhesion and motility. This hypothesis was recently shown to be true – verifying that IGFBP-2 also binds to α5β1 integrin in an RGD-dependent manner, resulting in decreased cell adhesion and proliferation (Schutt et al., 2004). These results are intriguing because the combination of these two properties does not make for a clear-cut phenotype with respect to tumor invasion (i.e., whether IGFBP-2 binding to α5β1 integrin is pro-invasive or anti-invasive). Further studies involving invasion assays are needed to show whether the decrease in cell adhesion resulting from the interaction of IGFBP-2 and α5β1 integrin results in an increase in tumor cell migration. Here, again, we may be seeing the juxtaposition of decreased cell growth and increased cell invasion (the result of the decreased cell adhesion), a scenario very similar to that found for the Rac-activator Tiam1 (Malliri et al., 2002), as described in the previous section. All of this together further reinforces the postulate that cells are either dividing or spreading, but never both simultaneously. The observations that lead to this belief were first seen in fibroblast cells, but are now apparent in colon carcinomas as well as in gliomas (Varner et al., 1995, 1996; Giese et al., 1996).

The mechanism by which IIp45 counteracts IGFBP-2 (as mentioned above in the section on the IGF system) remains to be identified. It is possible that the invasion inhibitory properties of IIp45 (Song et al., 2003) manifests through the competitive binding with IGFBP-2 because both IGFBP-2 and IIp45 have an RGD-sequence that has potential to bind integrins. That is, the binding of IIp45 at the RGD domain may prevent IGFBP-2 from binding to integrin and consequently prevent the propagation of downstream signals. Another possibility may be through a conformational change induced in IGFBP-2 following its binding with IIp45. Therefore, due to steric reasons, the binding IIp45 with IGFBP-2 could possibly change the exposure of the RGD domain in IGFBP-2 and thus affect the interaction with integrins.

As mentioned above, the IGF system regulates the expression of a number of MMPs (Long et al., 1998; Bredin et al., 2003; Zhang and Brodt, 2003), which are involved in the digestion of the ECM during cell invasion. There is now also evidence of the alternative processing of integrin subunits through MT1-MMP in tumor cells (Deryugina et al., 2002; Ratnikov et al., 2002). This not only points to a link between the pathways that regulate MMPs and integrins, it also points to the possibility that some MMPs play a more broad role in the invasion of tumor cells. This also suggests that the primary function of some MMPs may be the alternate processing of proteins rather than the breakdown of the extracellular barriers. This raises the possibility that other MMPs also play alternate roles in malignant cells, contributing overall to more cancerous phenotypes. Here, again, the IGF system may interact with the integrin system, though this time via an MMP-regulated intermediate step.

The EGF system also appears to have significant crosstalk with pathways of other systems regulating cell migration and invasion. This is important because not only is EGF signaling important in producing invasive phenotypes in many cancers, it also appears to be influenced by multiple pathways. In particular, the EGF receptor (EGF-R) appears to be a focal point for many cell signals, specifically G-protein coupled receptor (GPC-R) signaling, which transactivates EGF-R, thereby promoting cell invasion (Schafer et al., 2004). Further, in

**Fig. 3.** The EGF system appears to be a major intersecting point of pathways contributing to tumor invasion - an example of pathway crosstalk between various pathways systems. Specifically, at the EGF-R, signals from multiple receptors converge that influence tumor invasion.
generating an invasive phenotype, the signals downstream from EGF-R appear to utilize both the phosphatidylinositol-3-kinase (PI3-K) and extracellular regulated kinase 1, 2 (ERK 1,2) pathways (Price et al., 2002). Focal adhesion kinase (FAK), which has been linked to an increased cell invasion potential in many human cancers, has also been found to coordinate the EGF-stimulated migration of invasive tumor cells by enhancing EGF-stimulated JNK and ERK2 kinase activation (Hauck et al., 2001). Further, the EGF-R appears to interact with the α6β4 integrins of pathways if they should go awry. In general, however, which these pathways are interlinked means that normal every functional activity in the cell. The complexity with in the network of pathways that are linked to nearly signals orchestrating this phenomenon remain obscured uncontrolled signaling (e.g., the potential involvement of example, multiple pathways can be simultaneously mentioned here can contribute to tumor invasion. For found that one or more of the multiple systems reviewed in this area, we have Concluding remarks

Cell migration is a fundamental feature of normal growth and development. However, the physiological signals orchestrating this phenomenon remain obscured in the network of pathways that are linked to nearly every functional activity in the cell. The complexity with which these pathways are interlinked means that normal cell migration can be disturbed by various signaling pathways if they should go awry. In general, however, tumor invasion results from the de-regulation of a signal controlling cell movement and/or cell proliferation. In reviewing the current research in this area, we have found that one or more of the multiple systems mentioned here can contribute to tumor invasion. For example, multiple pathways can be simultaneously involved (e.g., the involvement of certain integrins with the IGFBPs). Further, feedback looping may explain uncontrolled signaling (e.g., the potential involvement of MMP-7 in IGF-IR signaling). Tumors can even utilize multiple pathways to achieve the same phenotype (e.g., invasion resulting from two different Rho signaling pathways) and potentially evade current anti-cancer therapies though this mechanism. Further, the crosstalk of pathways can dramatically alter phenotypes. Thus, whereas the pathways responsible for tumor progression were once thought to be relatively isolated, we are now learning that these pathways overlap and to a certain degree may even work in a unified fashion. Clearly, therefore, the signal transduction that determines a tumor’s invasive capacity is far more complex than originally thought and should not be viewed as a simple matter of cause and effect. On a positive note, our increasing appreciation and understanding of the complexity involved in this process is bringing to light new targets for therapy, which is the first step in cancer research.

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Tumor invasion signalling

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Tumor invasion signalling


