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Author for correspondence:
Albrecht Schwab
e-mail: aschwab@uni-muenster.de

Ion channels and transporters in tumour cell migration and invasion

Albrecht Schwab and Christian Stock

Institut für Physiologie II, Westfälische Wilhelms-Universität Münster, Robert-Koch-Strasse 27b, Münster 48149, Germany

Cell migration is a central component of the metastatic cascade requiring a concerted action of ion channels and transporters (migration-associated transportome), cytoskeletal elements and signalling cascades. Ion transport proteins and aquaporins contribute to tumour cell migration and invasion among other things by inducing local volume changes and/or by modulating Ca^{2+} and H^+ signalling. Targeting cell migration therapeutically bears great clinical potential, because it is a prerequisite for metastasis. Ion transport proteins appear to be attractive candidate target proteins for this purpose because they are easily accessible as membrane proteins and often overexpressed or activated in cancer. Importantly, a number of clinically widely used drugs are available whose anticipated efficacy as anti-tumour drugs, however, has now only begun to be evaluated.

1. Introduction

Tumour progression towards metastatic disease follows a well-defined sequence of events [1]. The metastatic cascade includes several critical steps that rely on the ability of tumour cells to migrate: local invasion of the affected tissue following the disruption of the basement membrane as well as intra- and extravasation of blood or lymph vessels (figure 1). Without their ability to move, tumour cells would not be able to metastasize. However, tumour cells do not necessarily act independently. They also can migrate collectively as a group [2]. Moreover, there is an intense mutual communication between tumour and stromal cells, and the tumour microenvironment that is typically characterized by local acidosis and hypoxia [3–5]. Thus, in pancreatic ductal adenocarcinoma (PDAC), reciprocal activation of stromal stellate cells and cancer cells strongly promotes tumour progression [6]. Metastases in PDAC may even contain tumour cells and pancreatic stellate cells [7]. Monitoring the collective invasion of co-cultured fibroblasts and squamous cell carcinoma cells revealed that the invading cell group is always led by fibroblasts [8]. Thus, the ability to migrate is equally important for cancer and stromal cells.

This review highlights the role of ion channels and transporters in the steps of the metastatic cascade that rely on the ability of tumour and stromal cells to migrate. Local fluctuations of the cell volume as well as pH and Ca^{2+} signalling evolved as common mechanisms linking ion transport proteins to the metastatic behaviour. We refer to three recent reviews [9–11] for a broader overview of ion transport in cell motility.

2. Ionic mechanisms of cell migration

Most malignant tumours are of epithelial origin. Hence, carcinoma cells have lost their epithelial polarization during epithelial–mesenchymal transition (EMT). Mesenchymal cells can detach and move away from the epithelial layer [12]. EMT involves a coordinated gene expression programme in association with the early steps of transformation which also can include proteins involved in ion transport. Thus, the ectopic expression of carbonic anhydrase (CAIX) is accompanied by a loss of cell–cell contacts. Subsequently, CAIX, pH-regulating transport proteins (e.g. NBCe1, AE2, NHE1, MCTs) and aquaporins are

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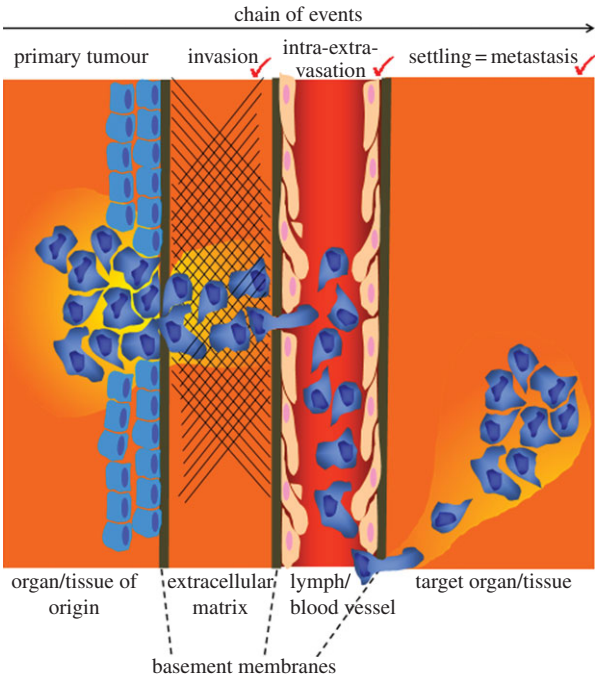

Figure 1. Involvement of cell migration in the metastatic cascade. During malignant transformation, cells of the primary tumour lose their contacts with the neighbouring, healthy cells and become motile. They degrade basement membranes, invade and cross extracellular matrices in order to eventually intravasate into blood or lymph vessels. Only few cells survive the intravascular milieu and adhere to the vessel wall at a distant site where they extravasate and invade to form a metastasis. Those steps of the metastatic cascade that rely on migration are labelled with a hooklet (tick symbols). (Online version in colour.)

reallocated to the cell front where they elicit functions relevant for cell migration (see below [13]).

Cell migration can be modelled as a repeated cycle of protrusion of the cell front and retraction of the cell rear. This involves a complex interplay of multiple components of the cellular migration machinery that are tightly regulated in space and time. Immediately at the leading edge, actin filaments polymerize while simultaneously depolymerizing towards the lamellipodial rear. This process is controlled by proteins that bind actin monomers, sever and branch existing filaments or nucleate the formation of new ones. The interaction of actin filaments with cytoskeletal motor proteins such as myosin generates force that is transmitted via focal adhesion complexes onto the surrounding extracellular matrix (ECM). In moving cells, new contacts are formed at the cell front, whereas others are released at the rear part. We refer to recent reviews that provide in-depth overviews of the cytoskeleton [14] and cell adhesion [15] in migrating cells. Cytoskeletal and cell adhesion dynamics are regulated by ionic mechanisms, and thereby depend on the activity of the respective transport proteins. These will be described in the following paragraphs with special emphasis on pH- and Ca^{2+}-dependence and the role of local changes of cell volume played therein. However, the involved transport proteins do not only regulate the intra- and extracellular pH and Ca^{2+} homeostasis. Many of them are pH- and/or Ca^{2+}-sensitive themselves. Moreover, intracellular Ca^{2+} and H^+ concentrations are physico-chemically coupled, and therefore cannot be changed entirely independently from each other [16]. The role of the mutual feedback of functionally cooperating transport proteins, the 'transportome', including their signalling pathways in cell migration has only begun to be appreciated. We will not discuss the interaction of K^+ channels with integrins as this is covered elsewhere in this issue [17].

(a) pH-dependent regulation of the cytoskeleton in tumour cell migration

Intracellular and extracellular pH homeostasis is particularly important in cancer as outlined elsewhere in this issue [4,5,18]. As the ionization state of all cellular and extracellular proteins including their function in (patho)physiological processes depends on pH, (directional) tumour cell migration is controlled by intra- and extracellular pH [19–23].

Cofilin regulates cell motility pH dependently [24]. It generates new sites of actin filament assembly by severing actin filaments and producing free barbed filament ends. This promotes dynamic actin polymerization and membrane protrusion at the cell front or at the tip of invasive structures [25]. The inhibition of cofilin activity by PI-(4,5)-P2 binding is removed upon an intracellular alkalinization [26]. The local intracellular alkalinization in the lamellipodium required for cofilin activation is generated by the activity of the Na^+/H^+ exchanger NHE1 that accumulates at the front of migrating tumour cells and fibroblasts [27–31]. NHE1 is upregulated in numerous tumours [22,32,33] and is required for motility of melanoma, breast cancer and cervix carcinoma cells [34]. Another way of pH-dependent regulation of cofilin involves cortactin. An NHE1-mediated increase in pH_i triggers the release of cortactin-bound cofilin. Cofilin then induces barbed end generation, thereby promoting actin polymerization [35]. Gelsolin is another actin-binding protein that is activated by an acidic pH and that controls actin assembly and disassembly [36]. Because NHE1 activity contributes to the generation of an intracellular pH gradient along the moving direction of migrating cells with more alkaline pH values in the lamellipodium [37], we assume that cofilin is more relevant for regulating actin dynamics at the leading edge, whereas gelsolin is more active at the acidic rear end. Finally, actin self-assembly and binding of myosin to actin is promoted by neutral or slightly acidic pH_i values [38,39]. These examples demonstrate that actin dynamics underlying the outgrowth of lamellipodia or invadopodia relies on an optimal intracellular pH environment [11,40], which, in turn, is adjusted by the activity of pH regulating H^+ (NHE1) and/or HCO_3^- transporters, possibly in cooperation with carbonic anhydrases or monocarboxylate transporters [13,32,41–43].

(b) Ca^{2+}-dependent regulation of the cytoskeleton in tumour cell migration

The intracellular calcium concentration ($[Ca^{2+}]_i$) has a great impact on the migration machinery of 'normal' (e.g. keratinocytes), tumour and stromal cells, too, because many of its elements such as myosin II [44], myosin light chain kinase [45], calpain [46], Ca^{2+}/calmodulin-dependent protein kinase II [47,48], focal adhesion kinase [49] or ion channels (e.g. K_{Ca} or TMEM16 channels) are Ca^{2+}-sensitive. Ca^{2+} regulation of cell migration involves a tight spatial and temporal control. In addition to a global front–rear gradient with $[Ca^{2+}]_i$ increasing towards the rear end of migrating cells [50,51], there are also local Ca^{2+} microdomains [45,52–54]. Spatial gradients of

$[Ca^{2+}]_i$ are superimposed by temporal changes, or oscillations of $[Ca^{2+}]_i$ that contribute to dynamic responses of the cellular migration apparatus [45,55]. One of the major mechanisms by which $[Ca^{2+}]_i$ signalling impacts on cell migration is the modulation of cytoskeletal dynamics.

α-Acitinin is an actin-binding protein controlling lamellipodial dynamics and directional migration [56]. It is Ca^{2+}-sensitive with an increase of $[Ca^{2+}]_i$, causing an inhibition of actin bundling activity [57]. Moreover, $[Ca^{2+}]_i$ is involved in the generation of a myosin-II-dependent contractile force during the retraction of the rear part of migrating cells [58]. On a smaller scale, retraction also occurs at the cell front. Here, local Ca^{2+} pulses of minute amplitudes that originate a few mircometres behind the leading edge induce the retraction of confined areas of the lamellipodium by activating MLCK and myosin-II-mediated contraction [45]. Interestingly, STIM1, a component of the store-operated Ca^{2+} entry (SOCE) channel, continuously appears close to the leading edge of PDAC cells [59]. Calcium-dependent development of mechanical force also has a large impact on cell adhesion which is detailed below. In neutrophil granulocytes, the ablation of TRPC6 channels caused a severe impairment of the cells to chemotax towards the KC (CXCL1) [60]. Local TRPM7-mediated Ca^{2+} sparks at the cell front are required for directional migration of fibroblasts towards a source of platelet-derived growth factor (PDGF) [53]. While the two latter studies were not performed with tumour cells, they are nonetheless instructive for tumour pathophysiology. First, they reveal signalling cascades that are also encountered in tumours such as PDAC [61]. Second, the ability of tumour or stromal cells to chemotax secures their mutual communication in response to paracrine growth factor stimulation in the tumour microenvironment. Chemotaxis of tumour cells also requires the activity of ion channels such as TRPC1 and/or $K_{Ca}3.1$ channels [62–65].

(c) pH-dependent regulation of tumour cell adhesion

Integrins are integral components of focal adhesions. Depending on their subunit composition, they mediate the interaction with different proteins of the ECM. Multiple integrins, such as $\alpha_2\beta_1$, $\alpha_5\beta_1$ or $\alpha_v\beta_3$, are pH-dependent in melanoma [19] and in other cells [66,67]. Increased adhesion at acidic extracellular pH values is explained by conformational changes that lead to an enhanced aviditity of the integrin headpieces to ECM proteins [67] or by a pH dependence of the mechanical stability of focal adhesions [68]. Conceptually, it is important that integrins protrude only 20 nm into the extracellular space [69]. Therefore, it is not surprising that the pericellular pH_e inside the glycocalyx is more important for cell adhesion than the pH of the extracellular bulk solution surrounding migrating melanoma cells [19,21]. The pericellular pH_e even confers asymmetry upon migrating tumour cells, because it is more acidic at the cell front than at the rear end [21,28]. The global pericellular front–rear pH gradient is superimposed by acidic pH_e nanodomains generated by NHE1 activity. Because these nanodomains are restricted to focal adhesions, we assume that NHE1 activity locally stabilizes the integrin-mediated interaction between cell surface and ECM [70]. In melanoma and in endothelial cells, this pericellular pH_e gradient is accompanied by a complementary intracellular pH gradient. pH_i is more alkaline at the cell front than at the rear part [37,71]. The alkaline pH_i at the cell front leads to a higher focal adhesion turnover owing to the lower affinity of talin for binding actin [40].

(d) Ca^{2+}-dependent regulation of tumour cell adhesion

The maturation and dynamic turnover of focal adhesions are modulated by the $[Ca^{2+}]_i$ [45,49,53,54,72]. This occurs in part because of a global gradient with $[Ca^{2+}]_i$ being usually higher at the rear end than at the front [50–53] which restricts the disassembly of focal adhesions by Ca^{2+}-sensitive family of calpain phosphatases to the rear part of migrating cells [73,74]. Alternatively, local Ca^{2+} elevations affect focal adhesion dynamics, possibly by mediating tyrosine phosphorylation of FAK [54]. Adhesion of cancer cells to the ECM is also mediated by invadopodia that share many similarities with podosomes found in 'normal' cells such as macrophages [75]. In microglial cells, the formation of invadopodia depends on the presence of extracellular Ca^{2+} whose transport into invadopodia is likely mediated by Orai1 [76].

(e) Cell volume dynamics during cell migration

As outlined above, cell migration can be viewed as a repetitive cycle of protrusion of the cell front and retraction of the rear part. The rear part often lags behind for quite some time before retracting at a much faster speed. Such shape changes are particularly prominent when cells are moving within a three-dimensional environment where tumour cells or stromal cells may extend processes as long as 100 µm before the cell body eventually catches up. This fast retraction of the rear part coincides with or follows an elevation of the $[Ca^{2+}]_i$ [55,77] which is likely to be caused by the activation of mechanosensitive Ca^{2+} channels. Their molecular identity has not yet been conclusively determined. TRPC1 [78], TRPM7 [53] and TRPV4 [79] channels are possible candidates. In addition to triggering the Ca^{2+}-dependent mechanisms outlined above, the elevation of $[Ca^{2+}]_i$ also leads to an activation of Ca^{2+}-sensitive ion channels such as $K_{Ca}3.1$ [80], $K_{Ca}2.3$ [81], ClC3 [48,82] or TMEM16A/ANO1 [83–85]. Studies of cell volume regulation revealed that cell shrinkage can be elicited by the simultaneous activation of K^+ and Cl^- channels [86]. Therefore, a hydrodynamic model was postulated according to which ion channels and transporters elicit local changes of cell volume that act in concert with cytoskeletal mechanisms underlying rear end retraction and/or the protrusion of the cell front [80,87,88]. This model was confirmed experimentally by several groups [89–93]. The observation that aquaporins are essential components of the cellular migration apparatus [94] lent further strong support to this model. Aquaporins provide the route for osmotically driven water influx or efflux, leading to local cell swelling at the cell front or shrinkage at the rear part, respectively.

3. Ionic mechanisms of tumour cell invasion

Tumour cell invasion is frequently linked to invadopodia [75]. They are sites of proteolytic degradation of the ECM, and thereby facilitate migration through a three-dimensional network of matrix fibres (figure 2). Traditionally, the role of invadopodia in tumour cell invasion is reflected by the presence of several proteases (e.g. MT1MMP, MMP2). The 'microscopic' NHE1-mediated acidification at the cell surface of lamellipodia and invadopodia facilitates the action of

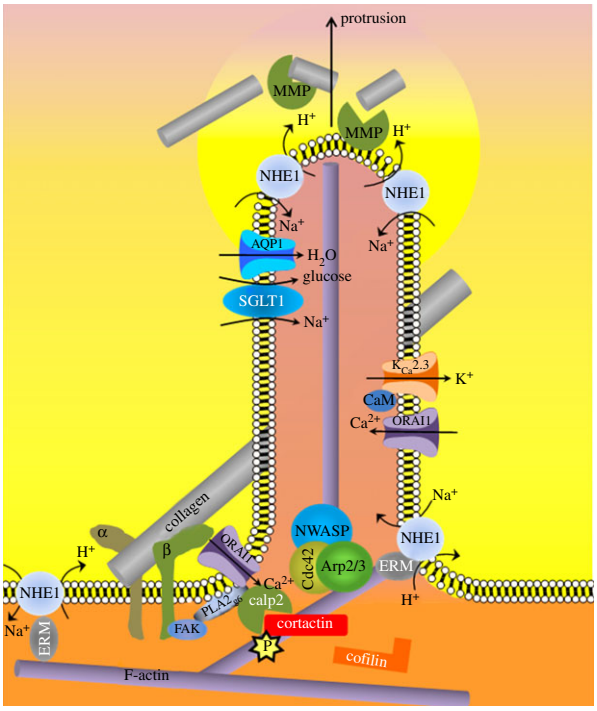

Figure 2. Hypothetical model of invadopodium formation involving pH, Ca^{2+} and volume regulation. Phosphorylation of cortactin (P) modulates the interaction between NHE1 and cortactin. Stimulated NHE1 activity increases pH_i and triggers the release of cortactin-bound cofilin. Cofilin then promotes actin polymerization. Cdc42, a small, pH-dependent Rho-GTPase, regulates actin polymerization by binding to the neural Wiskott–Aldrich syndrome protein (NWASP) which then activates the Arp2/3 complex. H^+ extruded by NHE1 causes an extracellular acidification, thereby facilitating the interaction between integrins and collagen and promotes the activity of matrix metalloproteinases (MMP). Lamellipodia/invadopodia outgrowth requires local volume increase that is mediated by water uptake through aquaporins (AQP) and possibly driven by the osmolytes glucose and Na^+ imported by the Na^+, glucose co-transporter 1 (SGLT1). By analogy with podosomes, Ca^{2+} influx through ORAI channels would occur and stimulate both calpain2 (calp2) to cleave cortactin and calmodulin to activate $K_{Ca}2.3$ channels. $K_{Ca}2.3$ could fine-tune Na^+ entry through the SGLT1 by keeping the membrane potential stable and controlling the amount of osmolytes entering the invadopodia. ORAI1 contributes to focal adhesion dynamics by co-localizing with PLA2g6. PLA2g6 supports the phosphorylation of the focal adhesion kinase (FAK) by activating ORAI1. (Online version in colour.)

pH-dependent proteases [28,95,96]. The activity of matrix metalloproteinase 2 (MMP2) requires the protonation of the substrate such as fibrinogen [97], and the expression of MMP9 is upregulated by an acidic extracellular pH [98]. Invasive behaviour of various tumour cells is also triggered by the expression of voltage-gated Na^+ channels (Na_V) [99]. They appear to cooperate with NHE1 during invasion of breast cancer cells by as yet undefined mechanisms [100] and increase the activity of cysteine cathepsins [101].

Based on the great similarity between podosomes and invadopodia, we assume that a similar Ca^{2+} dependence will also be found in cancer cells [76]. This view is supported by the fact that the ability of cancer cells to invade extracellular matrices could be related to the activity of Ca^{2+} influx channels such as TRPM7 or ORAI1 [102–104]. Finally, the activity of matrix metalloproteinases has also been linked to Ca^{2+} signalling [105,106]. The upregulation of MMP9 requiring Ca^{2+} influx can therefore be inhibited by blocking voltage-gated Ca^{2+} channels [107].

(a) Volume dynamics during tumour cell invasion

The ability of tumour cells to locally change their volume and shape, respectively, also facilitates their movement through the tortuous interstitium and through the wall of a blood/lymph vessel (intra-/extravasation). Ion channels and transporters thereby convey a means to the tumour cells to overcome mechanical barriers [108] which is particularly relevant when tumour cells invade the interstitium. Accordingly, migration of glioblastoma cells on a two-dimensional surface is not impaired when the $Na^+/K^+/2Cl^-$ cotransporter is inhibited while this is the case when they are invading the brain parenchyma [109]. Possibly, growth and protrusion of invadopodia are also supported by a mechanism similar to the one used by the intracellular pathogen *Cryptosporidium parvum* that induces SGLT1- and AQP1-driven membrane protrusions in the host cell [110] (figure 2). Glucose transporters are widely expressed in many tumour cells to ensure their metabolic supply [111]. Finally, their role in tumour cell invasion [112] may be due to the fact that the protrusion of lamellipodia is linked to glycolytic energy production [31]. Preclinical and clinical observations lend further support to the importance of cellular volume dynamics during invasion of tumour cells. Expression of aquaporins is associated with poor prognosis and metastatic relapse of a number of tumours (e.g. AQP1 overexpression in patients with lung adenocarcinoma; [113]).

4. Outlook and clinical perspectives

Studies from the past approximately 15 years provided proof of concept that ion channels and transporters are crucial for the metastatic behaviour of tumour cells. It is becoming increasingly clear that ion transport proteins do not act in an isolated manner on their own, but that they act in networks of functionally cooperating units [13,63,114,115]. This is reflected by the concept of the migration-associated transportome that we recently introduced [9]. It implies that ion transport signalling pathways such as pH, Ca^{2+} or cell volume are closely linked to each other. However, neither the pathophysiological significance of this crosstalk is well understood, let alone the interaction of ionic with kinase-based signalling pathways. For instance, it has not yet been investigated systematically how the altered expression of pH regulatory transporters in solid tumours affect the functional impact of other members of the migration-associated transportome and their crosstalk with growth factor signalling. Similarly, it is unknown whether transport proteins whose upregulation is mediated by hypoxia-induced HIF1α constitute 'functional units' involved in cell migration.

Extravasation of tumour cells in tumour-specific target organs is another step of the metastatic process for which the role of ion channels and transporters has not yet been investigated in detail. This process bears similarities to the recruitment of leucocytes from the bloodstream. It is supported by the cooperation of tumour cells with platelets and leucocytes [116]. Thus, it is reasonable to assume that tumour cells use similar ionic mechanisms to leucocytes (e.g. neutrophil granulocytes) in which Ca^{2+} influx via Orai1 plays an important role in the initial steps of recruitment [117]. Indeed, functional coupling between $K_{Ca}2.3$ and ORAI1 channels in lipid rafts seems to promote bone metastases of breast cancer cells [115]. Along the same lines, one could speculate that the reciprocal activation of integrins and $K_V11.1$ channels in tumour cells

contributes to their ability to extravasate, because $K_V11.1$ expression in acute myeloid leukaemia cells correlates with a higher probability of relapse [118].

Many of the transport proteins (e.g. $K_V10.1$) are not only involved in controlling cell migration and invasion, but also in other 'hallmarks of cancer' such as proliferation [114,119]. Thus, drugs that target members of the migration-associated transportome are likely to elicit more responses than just the inhibition of tumour cell migration and invasion. Combined effects such as inhibition of migration and proliferation by blocking $K_{Ca}3.1$ channels may be desirable [120,121], whereas the combined inhibition of migration and apoptosis by $K_V1.3$ channel blockade would certainly not be advantageous.

Because most tumour patients die of metastases the inhibition of the mechanisms underlying metastasis offers great therapeutic potential. Targeting tumour cell migration would therefore be a good choice because it is one of the prerequisites for metastasis. Indeed, migration has been targeted in order to treat chronic inflammatory diseases [122] which is another pathological condition strongly relying on the ability of (inflammatory) cells to migrate. Transport proteins that could qualify as a potential anti-migratory target include among others NHE1, $K_{Ca}3.1$ channels or Na_Vs. Migration and invasion of all tumours cells studied to date relies at least partially on the activity of one of these proteins [9]. Importantly, there are also small molecule inhibitors validated in phase III clinical trials ($K_{Ca}3.1$ blocker senicapoc [123] and NHE1 blocker cariporide [124]) or that are already widely used clinically such as amide-linked local anaesthetics that block Na_Vs. Presently it is being discussed whether the Na_V-mediated metastatic behaviour of tumour cells can be targeted by using amide-linked local anaesthetics during cancer surgery [125]. Similarly, the use of the K^+ sparing diuretic amiloride which is also an NHE1 blocker, can be envisaged [126]. Thus, there is an increasing number of functionally relevant ion transport proteins to be targeted. They are easily accessible because they are membrane proteins and often overexpressed or activated in cancer. Moreover, they have a long history of being drug targets in other medical fields such as cardiology, nephrology or anaesthesia. Alternatively, transport-associated proteins such as the tumour marker carbonic anhydrase IX could be targeted by specific antibodies [127].

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