Seminars in Cell & Developmental Biology 55 (2016) 111–118

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Chemotaxis during neural crest migration

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ARTICLE INFO

Article history:
Received 21 December 2015
Accepted 22 January 2016
Available online 25 January 2016

Keywords:
Chemotaxis
Neural crest
Collective migration
SDF1/CXCL12
VEGF
C3/C3aR

ABSTRACT

Chemotaxis refers to the directional migration of cells towards external, soluble factors along their gradients. It is a process that is used by many different cell types during development for tissue organisation and the formation of embryonic structures, as well as disease like cancer metastasis. The neural crest (NC) is a multipotent, highly migratory cell population that contribute to a range of tissues. It has been hypothesised that NC migration, at least in part, is reliant on chemotactic signals. This review will explore the current evidence for proposed chemoattractants of NC cells, and outline mechanisms for the chemotactic response of the NC to them.

Contents

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http://dx.doi.org/10.1016/j.semcdb.2016.01.031
1084-9521/

1. Chemotaxis

1.1. Definition

Cell migration is fundamental to many processes in development and disease, including embryonic morphogenesis, wound healing and the immune response [1]. This often involves cells responding to specific signals that guide their movement, either from mechanical stimuli, molecules bound to the extracellular matrix or soluble external factors [2–8]. Cell migration in response to gradients of the latter, called chemotaxis, has been widely studied and it is a well-established mechanism that provides directionality and persistence to migrating cells [7,9,10]. The chemotactic response of cells, in part, involves the polymerisation of actin at the leading edge and the accompanying formation of protrusions, and myosin-II-mediated contraction at the rear [11].

1.2. Criteria to define a chemoattractant

The first description of chemotaxis was made by Engelmann and Pfeffer in bacteria over a century ago [12,13]. Since then, repulsive [14,15] and attractive cues have been found for a variety of processes [1,9]. However, most factors are multifunctional on cell behaviour, which makes definitive demonstration of chemoattractant behaviour *in vivo* difficult. Nevertheless, some attributes of chemoattractants may be summarised as follows. Chemoattractants are generally transcribed, translated and secreted by the target tissue itself to where the responsive cells are migrating. These responding cells are required to express a receptor for the chemoattractant when temporally appropriate. Loss of the chemoattractant or its receptor should lead to failure of cells reaching the target region; instead, non-directional migration can be expected. *In vitro*, localised chemoattractants should cause chemotaxis and *in vivo*, cells should be diverted from their normal path by ectopic, localised sources of chemoattractant. Chemotaxis should be rescued by an exogenous ligand when the endogenous chemoattractant is lost, if placed into the region the cells would normal migrate toward. Chemotaxis requires that cells migrate up a concentration gradient of a soluble factor, so sufficient and consistent changes in the chemoattractant's concentration should be found to give rise to a detectable gradient. This last point is perhaps the most difficult to demonstrate due to technical limitations and that in some cases the gradient is generated *in situ* by the migrating cell [16]. Nonetheless, a fulfilment of these criteria is important to show that not only are the cells capable of being chemotactic towards the factor, but also that chemotaxis is actually happening *in vivo*. Altered migration in response to the external factor would otherwise demonstrate chemokinesis, the process by which factors simply promote or support migration, rather than providing directionality to the movement as in the case of chemotaxis, as seen in various cell types in physiology and throughout development [9,11].

2. The neural crest

2.1. Neural crest formation

The neural crest (NC) is a transient cell population exclusively found in vertebrates. It is initially induced at the neural plate border as a result of the interaction between the ectodermal neural plate and the epidermis [17]. Changes in the structure of the neural plate cells cause fusion of the neural folds, resulting in the formation of a closed neural tube and of NC on its dorsolateral aspect on each side [17,18]. Both the prospective neural plate and the prospective epidermis contribute to the NC [19,20]. After induction, NC cells undergo an epithelial-to-mesenchymal transition (EMT) [21], in which cells acquire motility, epithelial polarity is lost and there is a switch from more adhesive to weaker cadherin expression. These and the accompanying cytoskeletal changes mean that the NC cells leave the neuroepithelium of the dorsal neural tube and become highly migratory [18].

2.2. Neural crest derivatives

The NC are multipotent stem cells, able to differentiate into many cell types and extensively contribute numerous tissues (Fig. 1A) [22]. NC cells receive inductive signals from the neural tube, paraxial mesoderm and the overlying ectoderm as they migrate [23]. Their specification is a multistep process; their fate is based on these paracrine signals, as well as the time at which they migrate, their origin and the stream in which they are found [23–27]. The cranial NC contributes to the craniofacial mesenchyme, which includes cartilage, bone, teeth, cranial neurons, glia and connective tissue. Cardiac NC contributes to the cardiovascular system, developing into melanocytes, cartilage, connective tissue and pharyngeal arch neurons. Trunk NC gives rise to melanocytes, glia and neurons of the peripheral nervous system and epinephrine-producing cells of the adrenal gland. The vagal and sacral NC develops into the ganglia of the enteric nervous system and sympathetic ganglia.

3. Neural crest migration

3.1. Neural crest streams

After undergoing EMT, the NC becomes a highly migratory cell population, often likened to invasive cancers [18,28,29]. NC cell migration has been studied in a variety of vertebrate animal models, including *Xenopus*, zebrafish, chick, mouse [30] and even non-classical model organisms such as lamprey [31], hagfish [32] and turtle [33,34]. The NC migrate ventrally down the embryo, initially as a continuous wave away from the neural tube, but quickly splitting into discrete streams along stereotypical pathways to various sites (Fig. 1A). The cranial NC migrates along dorsolateral routes between the ectoderm and underlying paraxial mesoderm [35,36]. In chick and mouse, early trunk NC migrates ventrolaterally through the anterior sclerotome [37–40]. Trunk NC migrating later, which will become melanocytes, follow the dorsolateral path between the dermomyotome and dorsal ectoderm, with their migration affected by the structure of the somites [41]. However in zebrafish and *Xenopus*, melanocytes use both ventromedial and dorsolateral pathways [42,43].

The cranial NC divide into three streams that invade the segmented branchial arches (BAs), due to, at least in part, the repulsive signals of ephrins and class 3 semaphorins (Fig. 1B). Eph/ephrin signalling prevents NC cells from invading non-NC tissue and the caudal half of somites, thereby restricting them to the rostral half of somites in chick embryos [44,45]. Likewise, class 3 semaphorins contribute to NC segregation in the head, trunk and caudal regions of the sclerotome [46–51] by acting through plexin–neuropilin complexes expressed by the NC [47–49,51]. The mixing of NC from different streams is also prohibited because NC belonging to different streams express complementary Eph receptors and ephrin ligands [35].

3.2. Collective migration

NC displays a range of migratory behaviours depending on species and location within the embryo. Some exhibit a more individual migratory behaviour [52], whereas most of NC cells migrate together, either as chains, groups or even single sheets, in spite