Jawsfest: new perspectives on neural crest lineages and morphogenesis

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Summary

The neural crest is a fascinating population of cells that migrate long distances in the developing embryo to generate many different derivatives. It also occupies a central position in the origin and patterning of the vertebrate head, and has generated debates about issues such as cell programming versus plasticity and the role of cell death in early morphogenesis. These aspects of the field were revisited and discussed in a recent meeting organized to honour the retirement of Jim Weston and his contribution to the field

The neural crest is a fascinating population of cells that is generated in the vertebrate developing central nervous system. After undergoing a switch from a neuroepithelial to a mesenchymal phenotype, neural crest cells delaminate and migrate long distances along defined pathways to reach their final destinations. The neural crest gives rise to many different tissues and cells, including most of the peripheral nervous system and all of the pigment cells of the body, except for those of the pigmented epithelium of the retina. In the head, neural crest cells also give rise to the ectomesenchyme, from which craniofacial skeletal and connective tissues are derived (LeDouarin and Kalcheim, 1999). Its appearance in evolution, together with that of the epidermal placodes, is believed to have been crucial for the generation of the vertebrate head (Gans and Northcutt, 1983) (reviewed by Manzanares and Nieto, 2003).

To honour the retirement of Jim Weston and his contribution to developmental biology and to the neural crest field in particular, Chuck Kimmel and Judith Eisen from the University of Oregon (Eugene, OR, USA) together with Carol Erickson (University of California, Davis, CA, USA) organised a conference in June 2003 called 'Neural Crest: New Perspectives on Lineage and Morphogenesis', which was held on the beautiful Mount Hood in Oregon, USA. Much of the work of Jim Weston's laboratory over the years has focused on the segregation of cell lineages from the neural crest and the interactions of neural crest cells with the extracellular matrix (ECM) during their formation and migration in chick, mouse and, more recently, zebrafish. For many colleagues and friends it was a great opportunity to honour Jim and his career.

A brief overview on Jim Weston's love story with the neural crest

Jim Weston's extraordinary 40 year contribution to the neural crest field began in the late 1950s as a graduate student in J. P. Trinkaus' laboratory at Yale University where he pioneered autoradiographic techniques to lineage trace transplanted trunk neural crest cells in avian embryos (Weston, 1963). As a post-doc in Michael Abercrombie's laboratory at University College London, Jim turned his attention to the mechanics of directional cell migration and cell behaviour, which ultimately led to the identification of fibronectin (Yamada and Weston, 1974; Yamada and Weston, 1975). In his first faculty appointment at Case Western University in 1964, Jim's new laboratory focused on the environmental regulation of cell phenotype in neural crest cell culture assays and on how cell-cell and cell-substratum interactions affected cell behaviour (Cowell and Weston, 1970; Weston and Hendricks, 1972; Nichols et al., 1977). During this period, he and his colleagues developed an assay method to measure cell adhesion (Roth and Weston, 1967), which, for the first time, demonstrated the existence of cell adhesive properties that are specific and independent of cell morphogenetic behaviour. This assay provided the basis for the bioassays used later by other groups to isolate the molecules that are responsible for these cell adhesion properties.

In 1970, Jim moved to the University of Oregon where he continued to study the role of the ECM during neural crest cell migration (Weston et al., 1984). Here, he and his co-workers made some of the first monoclonal antibodies that were able to recognise distinct subpopulations of neural crest cells (Ciment and Weston, 1981; Ciment and Weston, 1982). These antibodies were instrumental in helping to discover that a finite subpopulation of neurogenic precursors existed in the trunk neural crest (Vogel and Weston, 1988; Vogel et al., 1993; Wakamatsu et al., 1998). In Oregon, Jim also began analysing neural crest cells in normal and mutant mice (Weston, 1983; Erickson and Weston, 1983; Morrison-Graham et al., 1990; Werhle-Haller and Weston, 1995), which led to the ideas he discussed at this meeting about ectomesenchyme [which expresses platelet derived growth factor receptors (PDGFRs, a family of receptor tyrosine kinases (RTKs)], and the demonstration that signalling from RTKs (such as Kit) exerts both trophic (survival, proliferation) and tropic (directed-migration) effects on crest-derived melanocyte precursors (Werhle-Haller et al., 2001). Jim was also involved in developing the University of Oregon's zebrafish research programme to study the molecular and genetic aspects of embryonic cell lineage diversification. He also initiated studies of the neural crest in this organism (Raible et al., 1992; Johnson et al., 1995; Johnson and Weston, 1995; Henion et al., 1996; Henion and Weston, 1997), addressing the issue of neural crest cell pluripotency. In recent work, his group has emphasised that the developmental fates of crest-derived cells depend not only on their interactions with the ECM, but also on cell-cell interactions between distinct crest-derived subpopulations (Wakamatsu et al., 2000; Maynard et al., 2000). Although Jim remained in Oregon until his retirement this year, his sabbaticals, particularly in Naples, Cambridge, Rehovot, Kyoto, London and Paris, have satisfied his appetite for travel and have ensured his keen observation and scientific intellect have been appreciated all over the world.

Does the non-neural ectoderm produce ectomesenchyme?

Jim was not only honoured at this meeting but he also

presented provocative new data. He proposed that not only the neural ectoderm (as is believed) but also the non-neural ectoderm undergo epithelial to mesenchymal transitions (EMT) in the embryonic head to give rise to migratory cells. These cells derived from the non-neural ectoderm would, according to Jim, give rise to at least some of the ectomesenchyme that is thought to be exclusively derived from the neural crest that delaminates from the neural epithelium. This proposal is based on morphological analyses and on the overlapping expression of PDGFRα (a marker of both mesodermally derived mesenchymal cells and ectomesenchyme) and E-cadherin (a marker of non-neural epithelia) in some cells of the cephalic neural folds (Fig. 1). These cells exhibit the hallmarks of an EMT, including changes in cell shape and the loss of cell-cell adhesion molecules. Indeed, E-cadherin expression is still detected in these cells but it is decreased and confined to the cytoplasm, as if it was being degraded and not replaced at the cell membrane. In agreement with this, Snail, one of the major regulators of EMT, which directly downregulates E-cadherin transcription (Cano et al., 2000) is expressed in the neural folds and in the cells that delaminate from them (Fig. 1). However, long-term fate-mapping studies, which are under way, are required to validate this new theory.

Neural crest-inducing signals: what is new?

The search for neural crest-inducing signals continues unabated. The main players to date are Wnt, bone morphogenetic protein (BMP) and fibroblast growth factor (FGF) signalling, all of which can induce neural crest cells (reviewed by Knecht and Bronner-Fraser, 2002). It is not clear whether these signals act synergistically or whether an interface between these genetic pathways is required to induce neural crest formation.

An intermediate level of BMP signalling has been proposed to induce neural crest in both *Xenopus* and fish (reviewed by Aybar and Mayor, 2002). Interesting new data indicate that the BMP signalling target, Msx1, is induced only by an intermediate level of BMP signalling in *Xenopus* and that Msx1 lies upstream of early neural crest markers, such as Snail and Slug (Roberto Mayor, University of Chile, Santiago, Chile). Evidence that BMP signalling induces Slug expression has been confirmed in the chick, with the characterisation of Smad-binding sites in the *Slug* promoter (Yoshio Wakamatsu, Tohoku University, Japan). Interestingly, as also discussed by Wakamatsu, BMP can apparently induce Slug expression in a much broader domain, which then becomes restricted to the neural crest prospective territory (the dorsal edge of the neural plate) by Sox2, which is proposed to function as 'anti-crest'.

Both in *Xenopus* (as discussed by Mayor) and in zebrafish [as discussed by Judith Eisen (University of Oregon, Eugene, OR, USA)], the activation of Notch signalling is required for neural crest formation. In the frog, it has been proposed to play an instructive role, whereas in zebrafish, Notch signalling only indirectly promotes neural crest formation through the inhibition of neurogenin 1. In agreement with this, in the zebrafish mutant *mindbomb* (which encodes an E3 ubiquitin ligase) all Delta/Notch signalling is blocked, and there are no pigment cells or neural crest-derived neurones in the trunk. Instead, there is an increase in the neurogenin-dependent sensory Rohon-Beard neurones, and lineage studies have also highlighted that dorsal root ganglia and Rohon-Beard neurones

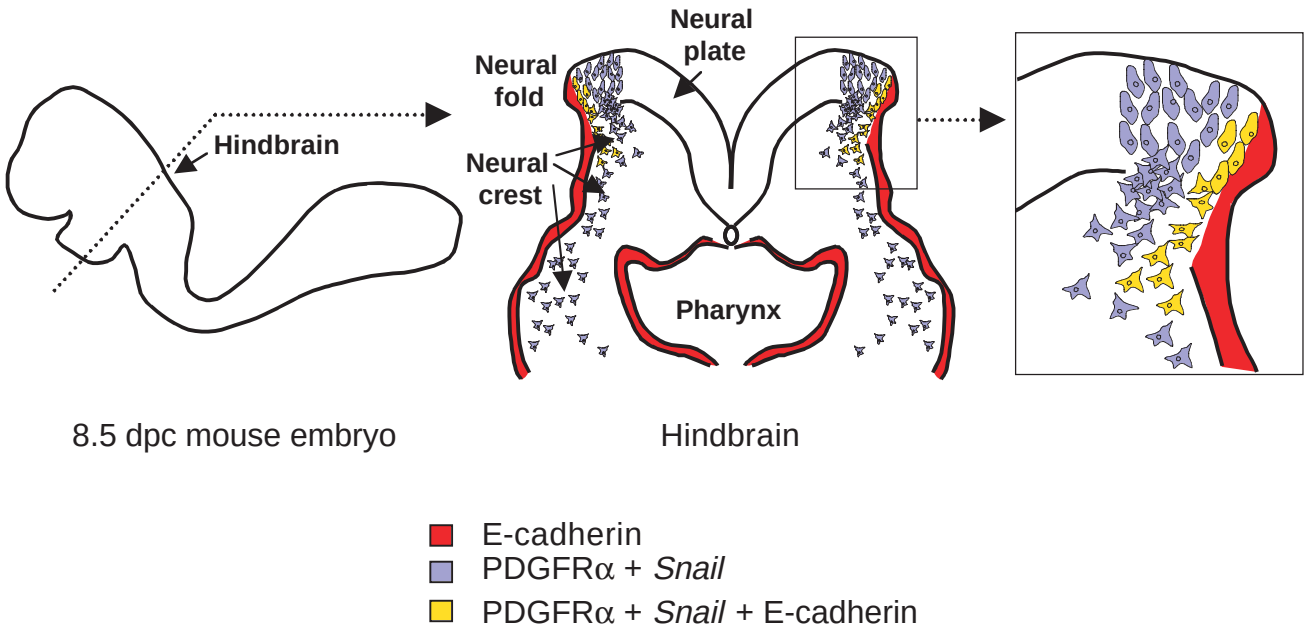

Fig. 1. Cells in the neural folds of the mouse embryo undergo an epithelial-to-mesenchymal transition (EMT) to become migratory and give rise to the neural crest. According to Jim Weston's provocative new theory, cells delaminate from the neural epithelium and also from the non-neural ectoderm. The cell population that is proposed to originate from the non-neural ectoderm is shown in yellow and is characterised by the overlapping expression of platelet-derived growth factor α (PDGFRα, a mesenchymal cell marker) and low levels of cytoplasmic E-cadherin (a marker of non-neural epithelial cells), the latter being compatible with the non-neural origin of these cells. Its mesenchymal phenotype is also compatible with the presence of Snail, a zinc-finger transcription factor that is known to trigger the EMT (Nieto, 2002). Lineage analyses are necessary to confirm the origin of these cells and to assess the nature of the derivatives that they produce. dpc, days post coitum.

are not lineally related (Eisen). In the avian non-neural ectoderm, Notch signalling seems to downregulate Slug expression and to activate BMP4, which in turn, induces Slug in the adjacent neural ectoderm (Wakamatsu).

BMP signalling has also been implicated in the delamination of the trunk neural crest in the chick embryo. A gradient of BMP activity is generated along the anteroposterior axis by a countergradient of its inhibitor Noggin (Sela-Donenfeld and Kalcheim, 2001). In parallel, a cell-autonomous mechanism controls the cell cycle in such a way that most of the migratory crest cells are in the S phase of the cell cycle (Chaya Kalcheim, Hebrew University, Jerusalem, Israel). As discussed by Angela Nieto (Cajal Institute, Madrid, Spain), it is possible that Snail family members play a role in the cell-cycle synchronisation process. New data also suggest that Wnt signalling mediates the BMP-dependent effects on the cell cycle progression of the neural crest (Kalcheim). In fact, Wnt signalling is involved in multiple phases of neural crest development in different species. In zebrafish, as discussed by David Raible (University of Washington, Seattle, WA, USA), Wnt8.1 is important for neural crest induction, and other Wnt family members subsequently cooperate with the previously Wnt8.1-induced Sox10 to activate the expression of the melanoblast specific factor Mitf-a (microphthalmia-associated transcription factor).

Preprogrammimg versus plasticity

A great deal of this field's time and effort in the past two decades has focused on the mechanisms of neural crest patterning and the controversial topic of whether neural crest cells are pre-programmed prior to their emigration from the neural tube or whether they are patterned primarily by the environment they come into contact with during their migration. As Andrew Lumsden (King's College, London, UK) argued, neural crest pre-programming allows a registration to be maintained between distinct axial tissues, such as the hindbrain and branchial arches, during head development. Pre-programming or autonomy appears to be crucial for the specification and migration of melanoblasts in the trunk. Melanoblasts are neural crest-derived cells that leave the neural tube later than the future neuronal derivatives, they are lineage restricted when they migrate and are the only neural crest-derived cells that can take the dorsolateral pathway in the trunk (Erickson and Goins, 1995). Carol Erickson (University of California, Davis, CA, USA) suggested that this may be due to the differential response of melanoblasts to the ephrins that are localised to this pathway. Whereas neuronal and glial precursors are prevented from migrating by their interactions with ephrins, melanoblasts are stimulated to migrate upon binding to them (Santiago and Erickson, 2002).

As Paul Trainor (Stowers Institute, Kansas City, MO, USA) discussed, neural crest plasticity and independent gene regulation within the neural tube and neural crest offer a degree of developmental flexibility that permits region-specific differentiation, and that possibly provides an evolutionary mechanism for diversifying neural crest cells and, consequently, craniofacial morphogenesis (see Trainor and Krumlauf, 2001). This plasticity is important in both tooth differentiation (Paul Sharpe, King's College, London, UK) (see James et al., 2002) and also in cranial neural crest migration. The independent gene regulation of neural tube cells in the migratory neural crest allows tooth differentiation to be independent of Hox gene expression. Similarly, plasticity may explain the subtle mixing that is observed between neural crest cells of distinct branchial arch streams that express a differential code of Hox genes, as demonstrated via the power of in ovo time-lapse video microscopy in chick embryos (Paul Kulesa, Stowers Institute, Kansas, USA). Clearly, there is evidence to support both prepatterning and plasticity, and the consensus is that neural crest patterning relies on a balance between the signals that are acquired by the neural crest in the neural tube during their formation and those that come from their environment, which influence their pathways of migration and specific differentiation fates. The precise mechanisms eliciting these signals and how the cells balance their influence differ between species and even between different neural crest cell lineages. Drew Noden (Cornell University, Ithaca, NY, USA) commented that neural crest patterning is like a boxing match: a lot of punches are being thrown and it may not be the first punch that is most important but rather the combination as a whole that counts.

The power of imaging

It was very fitting, given the history of Jim Weston's contribution to the roles of the ECM in neural crest patterning that advances in molecular biology combined with sophisticated imaging have turned the tide of the field back to the environmental influence of tissues on neural crest cell patterning. Tissues that, together with the neural crest, contribute to the branchial arches, such as the ectoderm (Sharpe), mesoderm (Trainor) and endoderm (Tom Schilling, University of California, Irvine, CA, USA), all play specific roles in neural crest cell patterning. The endoderm, for example, appears to be crucial for the skeletogenic differentiation of cranial neural crest cells in both zebrafish and in chick (see David et al., 2002; Ruhin et al., 2003). The analysis of the *van gogh* (Tbx1) mutant in zebrafish indicates that the endoderm may also control the dorsoventral patterning of the neural crest in the pharyngeal arches (Shilling) (Piotrowski et al., 2003). The challenge for the future will be to understand how signals from each of the distinct tissues are coordinated with the neural tube and neural crest to ensure proper craniofacial morphogenesis.

Some of the components of the ECM that are important for focal adhesions and neural crest cell migration include fibronectin and integrins, and beautiful data were presented on the dynamics of integrin turnover at the leading-front versus the lagging-rear of the migratory melanoblast (Berni Wehrle-Haller, University Medical Centre, Geneva, Switzerland). Benjamin Geiger (Weizmann Institute, Rehovot, Israel) discussed the existence of a coat of hyaluronan that is several micrometers thick and that is associated with the cell surface, which modulates the first steps of cell adhesion to the substrate (Cohen et al., 2003). This coat can also block adhesion or interfere with the interaction of soluble molecules with the cell membrane. It is still not known what the fate of this hyaluronate is after the transition to integrin-mediated adhesion.

As already mentioned, fibronectin was first isolated in Jim's laboratory some 30 years ago (Yamada and Weston, 1974), and Ken Yamada (NIH, Bethesda, USA) discussed the role and regulation of cell surface fibronectin expression during branching morphogenesis in epithelia. Fibronectin induces a

local replacement of a cell-cell adhesion complex with cell-ECM complexes, promoting the formation of clefts during the branching process (Sakai et al., 2003).

Another controversial issue discussed at the meeting was that of the importance of the apoptotic elimination of pre-migratory neural crest cells in odd-numbered rhombomeres in the hindbrain. Odd-rhombomere cell death is prevalent in avians, where it may serve an evolutionary purpose. Indeed, inhibition of this cell death in the chick embryo leads to ectopic sites of muscle attachment that are reminiscent of those present in other species that do not undergo this apoptotic process (Lumsden) (see Ellies et al., 2002). In relation to this, although cell death is observed in the neural tube of mouse embryos (Trainor) and very little can be detected in zebrafish (Schilling), the process is extremely dynamic in these vertebrates and it is difficult to associate to specific rhombomeres. As discussed by Angela Nieto, the differential expression of Snail family members may account for the resistance of neural crest cells to apoptotic signals.

The power of in ovo time-lapse imaging was again highlighted in movies that showed that when an odd rhombomere crest cell occasionally enters the normally inhibitory mesenchyme, its filopodia rapidly collapse (Kulesa). By contrast, during normal neural crest migration, the cells dynamically sample their environment through extensive filopodial extension and retraction, which reflect the interactions that occur between migrating neural crest cells and their surrounding tissues. Similar to early migratory midbrain and posterior hindbrain derived neural crest cells (Kulesa), vagal neural crest cells, which give rise to the enteric nervous system (ENS), also migrate in chain-like arrays in the gastrointestinal tract (Don Newgreen, University of Melbourne, VIC, Australia). Yet, timelapse videomicroscopy using green fluorescent protein driven by the Ret promoter to label neural crest cells in this tissue, showed that individual cell pathways in the intestinal microenvironment are dynamic, rapidly changing and far from unidirectional. Glial cell line-derived neurotrophic factor (GDNF) acts in the gut mesenchyme as a chemoattractant to guide presumptive ENS Ret-expressing neural crest cells, while endothelin 3 prevents the GDNF-induced neuronal differentiation.

No conference these days is complete without a reference to stem cells. Based on their broad differentiative fates and limited capacity for self-renewal, neural crest cells are often considered by many to be a stem cell-like population. Therefore, it was interesting to hear from Paul Sharpe that trunk neural crest cells, embryonic and foetal stem cells and adult neural stem cells are competent to make the hard mesenchymal tissues of the head, such as cartilage, bone and the odontoblasts of teeth, when exposed to the oral epithelium.

Conclusion

Despite decades of intensive research, we still have a long way to go to in order to fully understand neural crest development. This is particularly true with respect to the environmental signals that influence neural crest cell migration and differentiation, and the mechanism of neural crest evolution and their subsequent effects on craniofacial morphogenesis. Zebrafish mutagenesis has accelerated our understanding of neural crest cell patterning, and similar ongoing focused screens in mice should add significantly to the field in the immediate future. With the chicken genome project due for completion early next year, neural crest research should still be full of surprises for years to come and will maintain Jim's status as 'one of the guardians of the neural crest temple' (Jean Paul Thiery, The Curie Institute, France).

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