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Review

Comparative embryology of the carotid body☆

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ABSTRACT

Vertebrate carotid bodies and related structures (branchial arch oxygen chemoreceptors in fishes, carotid labyrinth in amphibians, chemoreceptors in the wall of the common carotid and its branches in birds) develop in embryos when neural crest cells, blood vessels, and nerve fibers from sympathetic and cranial nerve ganglia invade mesenchymal primordia in the wall of the 3rd branchial arch. This review focuses on literature published since the 1970s investigating similarities and differences in the embryological development of 3rd arch oxygen chemoreceptors, especially between mammals and birds, but also considering reptiles, amphibians and fishes.

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1. Introduction

Classical anatomical embryology of the carotid body (CB) has received considerable attention over the last century and produced many excellent research papers, monographs, and reviews, for example: Adams (1958) (comparative morphology of the CB); Batten (1960) (contribution of epidermal placodes to CB development), Murillo-Ferrol (1967) (morphological development of the avian CB); Rogers (1965) (uncertain embryonic origins of CB, especially glomus cells), and Smith (1924) (morphological interactions of third arch mesoderm, blood supply, sympathetic trunk, glossopharyngeal, and vagal nerves in CB development). The present review includes main points from these earlier works, but focuses on developments from 1970 onward, when new methods such as the development of chick-quail chimeric embryos (Le Lievre and Le Douarin, 1975), and histochemical, immunohistological, and transgenic animal studies added significantly to the knowledge of CB embryogenesis.

1.1. Evolutionary background

The oxygen-sensitive CB glomus cells of higher vertebrates and similar glomus-like cells in the 3rd branchial arch derivatives of lower vertebrates are derived from the neural crest (reviewed by Milsom and Burleson, 2007). Gans and Northcutt in their paper "Neural crest and the origin of vertebrates: a new head" (1983) proposed that the extensive cephalic reorganization that first appeared in agnatha and gnathostomes (vertebrate ancestors of extant fishes, amphibians, reptiles, birds, and mammals) was a radical evolutionary specialization of the first vertebrates for life as active predators. These specializations included articulated jaws (except in agnatha) for prey capture and ingestion, enhanced respiratory and circulatory systems to support high metabolic rates, and a variety of paired sense organs (including carotid bodies, and lateral line organs) to support an active lifestyle and enable prey detection. According to Gans and Northcutt's theory, neural crest cells and associated epidermal placodes played key roles in this transformation.

Neural crest cells (NCC) are transitory features in vertebrate embryos formed along the mediodorsal lateral ridges of the neural tube during neurulation (reviewed by Dupin and Sommer, 2012; Le Douarin, 1986). During embryogenesis, multipotent NCC migrate according to their position along the border of the neural plate, and undergo transformation into other cell types that produce many characteristic structures of vertebrates, including the craniofacial skeleton, jaw, melanocytes, smooth muscle cells of the branchial arch arteries and their derivatives, and most of the peripheral nervous system including the sympathetic and parasympathetic autonomic ganglia, enteric ganglia, satellite glial cells in ganglia, dorsal root ganglia, Schwann cells, adrenal medullary chromaffin cells, and some paired cranial sense organs including the carotid bodies (Dupin and Sommer, 2012).

Epidermal placodes (EP) like NCC are ectodermal derivatives. They form adjacent to the neural plate, and migrate during embryogenesis, but unlike NCC, EP form only in the head region of the neural tube (Batten, 1960; Gans and Northcutt, 1983; Graham and Shimeld, 2012). Epidermal placodes help form ears, eyes, and nose, and sensory ganglia of many cranial nerves. The nodose ganglia of the vagi (X) and the petrosal ganglia of the glossopharyngeal nerves (IX) have a dual origin from EP and NCC (Le Douarin, 1986). Because the nodose and petrosal ganglia provide innervation to the avian

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and mammalian CB, respectively, NCC and EP derivatives are both required for CB embryogenesis.

1.2. Neural crest origin of the carotid bodies in birds

Early attempts to study the migration and fate of NCC relied on detecting endogenous markers or applying exogenous markers to early stage NCC while they were aggregated near the neural plate, then observing the movement of marked NCC in the developing embryo (*reviewed by* Chai et al., 2000; Jiang et al., 2000; Le Douarin, 1980, 1986). Such techniques posed problems because the marked cells generally lost label intensity as cell division occurred, or cells ceased expressing an endogenous marker during differentiation. This problem was solved in 1972 when Le Douarin and coworkers (*reviewed by* Le Douarin, 1980, 1986; Le Lievre and Le Douarin, 1975) developed a stable avian chimeric system for permanently marking and tracking the migration and fate of NCC. They exploited the fact that Japanese quail cells (*Coturnix coturnix japonica*) have a large concentration of heterochromatin in their interphase nucleoli, which appears clearly different from the even distribution of heterochromatin in chicken cells (*Gallus gallus*). This difference was visible with light or electron microscopy, and the grafted cells and their NCC derivatives retained distinctive heterochromatin even after differentiation. An "isotopic–isochronic" grafting procedure was developed involving the removal of donor neural crest primordium (segments of neural tube and neural fold, see Fig. 1 in Le Douarin, 1980) from quail embryos, and grafting this to recipient chicken embryos at the same developmental stage (isochronic), and at the same somatic position along the embryonic axis (isotopic). The recipient chick's own neural primordium was removed just prior to grafting the donor primordium. Quail-chick chimeras developed normally, and the transplanted NCC migrated and differentiated normally, a process that could be followed in serial sections by observing the characteristic quail cell heterochromatin. These chimeras were the first stable system for tracking the fate of NCC in developing embryos and were used to show the neural crest origin of avian CB glomus cells (Le Douarin, 1980, 1986; Le Lievre and Le Douarin, 1975; Pearse et al., 1973). For many years it was assumed that the same NCC origin of CB glomus cells was also likely true for other vertebrates.

1.3. Neural crest origin of CB in mammals

Use of the avian technique of chimeric fate-mapping NCC was not feasible in mammals. However, equivalent information about the NCC origin of mammalian CB has been obtained with transgenic mice by exploiting the promoter *Wnt1* (a proto-oncogene uniquely expressed by migrating NCC) to control expression of a reporter gene for tracking NCC migration and fate (Chai et al., 2000; Jiang et al., 2000). Pardal et al. (2007) analyzed CB development using a *Wnt1 Cre*/floxed *LacZ* transgenic mouse, in which NCC cells and their derivatives permanently expressed β-galactosidase as a reporter, and reacted positively to X-gal upon histological examination.

With the *Wnt1* Cre/floxed *LacZ* transgenic mouse model, Pardal et al. (2007) showed that neural-secretory glomus (type I) cells and glial-like sustentacular (type II) cells in the mammalian CB are both of cranial neural crest origin. Furthermore, they showed that exposure to chronic hypoxia would induce sustentacular cells in mature mice to transform into glomus cells, a stimulus long known to cause glomus cell hyperplasia in the CB. Since these experiments showed that some CB type II cells retain the stem cell-like multipotency of the NCC from which they derive, Pardal et al. (2010) proposed that the carotid body is a neurogenic niche in the peripheral nervous system. Retained multipotency of CB type II cells not only explains the physiological ability of the immature and adult CB to undergo hyperplasia in chronic hypoxia, it may also explain rarer tumorous growths (chemodectomas) of the CB, which interestingly occur more often in chronically hypoxic persons living at high altitude (Pardal et al., 2010). There is also evidence that autotransplantation of CB tissue into the substantia nigra of Parkinsonian animal models can relieve the motor symptoms associated with dopamine deficiency (a potential treatment for Parkinsonism). However, it is presently unclear whether these promising results are due to the transplanted CB stem cells transforming into glomus cells and producing dopamine, or due to the transplanted CB cells producing paracrine substances, such as glial derived neurotrophic factor, which could directly stimulate increased dopamine production from the existing nigro-striatal pathway (Pardal et al., 2010; Villadiego et al., 2005).

2. Development of the mammalian and avian CB: overview

The first visible sign of CB development in both mammals and birds is a condensation of mesenchymal cells in the wall of the 3rd aortic arch artery (Rogers, 1965; Kameda, 1994; Kondo, 1975; Murillo-Ferrol, 1967; Smith, 1924). In mammals, thickening of the 3rd arch arterial wall occurs adjacent to the primordia of the superior cervical ganglion on the sympathetic trunk. In birds, the 3rd arch wall thickening occurs adjacent to the primordia of the vagal (nodose) ganglion and vagal recurrent nerve. At the conclusion of mammalian embryonic development, the bilateral carotid bodies lie in the upper neck at the carotid bifurcation and are innervated by the carotid sinus nerves carrying afferent fibers to the petrosal ganglia of the glossopharyngeal nerves (cranial nerve IX), and sympathetic (efferent) nerve fibers from the superior cervical ganglia. Conversely, the fully developed bilateral avian carotid bodies lie within the thoracic cavity next to the common carotid artery just cranial of the origin of the subclavian artery, and adjacent to the thyroid, parathyroid, and ultimobranchial glands. They are innervated by fine nerve branches arising from the adjacent vagus (cranial nerve X), vagal nodose ganglia, vagal recurrent nerves, and nerve fibers from the sympathetic trunk (arising at the level of the 14th cervical sympathetic ganglion in chicken, Kameda, 2002).

2.1. Human CB embryology

Hervonen and Korkala (1972) studied the CB microanatomy of human midterm fetuses, gestational age 14–16 weeks (full term is 38 weeks), and described the carotid bodies as remarkably mature with structural characteristics like those of adult carotid bodies. Glomus (Type I) cells were plentiful and contained numerous dense-cored vesicles that exhibited characteristic monamine fluorescence after glutaraldehyde fixation. Sustentacular (Type II) cells lacking dense-cored vesicles surrounded the glomus cells. Axon terminals were seen in apparent synaptic contact with glomus cells, and axon bundles were in close contact with sustentacular cells. Blood capillaries arose directly from the carotid artery and formed an anastomosing network around which the other cell types were organized. The capillaries were also surrounded with adrenergic nerves.

Smith et al. (1993) studied the innervation pattern of CB in human fetuses and reported that one nerve bundle touched the CB primordia at 10 weeks, followed by another at 13 weeks, and both bundles then formed a plexus around the CB with some fibers entering the superficial region of the CB primordium. At 19 weeks nerve fibers had penetrated to the deepest part of the primordium and at 23 weeks synapses were seen between nerve fibers and glomus cells.

Korkala and Hervonen (1973) and Scraggs et al. (1992) evaluated the developmental time-course of carotid bodies from human fetuses at gestational ages ranging from 7 to 22 weeks and 13–19

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