Int. J. Dev. Biol. 58: 303-306 (2014)
doi: 10.1387/ijdb.140143dr

THE INTERNATIONAL JOURNAL OF DEVELOPMENTAL BIOLOGY
www.intjdevbiol.com

Epithelial-mesenchymal interactions: a fundamental Developmental Biology mechanism

DOMENICO RIBATTI* and MARCELLO SANTOIEMMA

Department of Basic Medical Sciences, Neurosciences and Sensory Organs, University of Bari Medical School, National Cancer Institute "Giovanni Paolo II", Bari, Italy

ABSTRACT Interactions between epithelium and mesenchyme are common features of early stages of morphogenesis in different organs. In this historical review article, we retrospectively analyze the most important contribution to the definition and characterization of these interactions in three different organogenetic systems, including kidney, lung and limb bud. Tubule formation in the kidney is an example of an organogenetic event which involves interaction between the ureteric epithelium and the underlying mesenchyme that, in turn, induces the branching of the ureteric epithelium. In contrast, in lung organogenesis, interactive signaling occurs between the endodermal epithelium and the mesenchyme, leading to an alveolar structure. Finally, limb bud development results from a series of epithelial-mesenchymal interactions between the mesenchymal cells of the lateral plate mesoderm and the overlying ectodermal cells.

KEY WORDS: *embryology, epithelia, kidney, limb bud, lung, mesenchyme*

Introduction

All organs develop and consist of an epithelium and a mesenchyme that during the early stages of morphogenesis share common morphological features (Grobstein, 1967). In some of these interactions, epithelium is able to induce differentiation of the mesenchyme and vice versa, and play an instructive role mediated by differential activation of genes in responding epithelial cells. Epithelial-mesenchymal interactions were described in detail by experimental embryologists as early as in the 1950's and 1960's.

Interactions between epithelium and mesenchyme are mediated by soluble factors, through direct cell-cell contact, and are under the influence of the extracellular matrix (ECM) (Grobstein, 1954), which changes its organization (Ekblom *et al.*, 1981) and adhesive properties (Ekblom *et al.*, 1980), and by diffusion of soluble factors. Direct cell-cell interactions between mesenchymal and responding epithelial cells have been observed during mammary gland development (Sakakura, 1991). Moreover, growth factors and ECM molecules may interact in the signaling of mesenchymal-epithelial interactions.

Grobstein (1956) (Fig. 1) and others (Saxen *et al.*, 1976, Slavkin and Bringas, 1976), found in the kidney and teeth that induction is mediated by soluble paracrine factors also in the presence of a Millipore filter between the epithelium and mesenchyme. Proteins, such as Nodal and Activin diffuse over a long distance and can induce different sets of genes at different concentrations (Gurdon *et al.*, 1994, Gurdon *et al.*, 1995), while others, including Wnt, Vg1, and BMP4 proteins, however, act over a short distance (Jones *et al.*, 1996, Reilly and Melton, 1996).

Another feature of induction is its regional specificity. For example, the chick epidermis secretes proteins that signal the underlying dermal cells to form condensations, which, in turn, secrete soluble factors able to interact with the epidermis and to induce the formation of specific cutaneous structures (Nohno *et al.*, 1995, Ting-Berreth and Chuong, 1996).

In this historical review article, we retrospectively analyze the most important contribution to the definition and characterization of these interactions in three systems, including kidney, lung, and limb bud.

Reciprocal interactions of developing kidney tissues

The development of the kidney starts when the ureteric bud, a local evagination of the Wolffian nephric duct, grows into metanephritic mesenchyme. The epithelium of the ureter forms a network of tubules that are embedded in the mesenchyme, part of which

Abbreviations used in this paper: AER, apical ectodermal ridge; BMP, bone morphogenetic protein; FGF, fibroblast growth factor; GDNF, glial-derived neurotrophic factor; GAG, glycosaminoglycan; TGF-β, transforming growth factor beta.

***Address correspondence to:** Domenico Ribatti. Department of Basic Medical Sciences; Neurosciences and Sensory Organs; University of Bari Medical School; National Cancer Institute "Giovanni Paolo II"; Bari, Italy. e-mail: domenico.ribatti@uniba.it

Accepted: 2 September 2014. *Final, author-corrected PDF published online:* 30 September 2014

ISSN: Online 1696-3547, Print 0214-6282

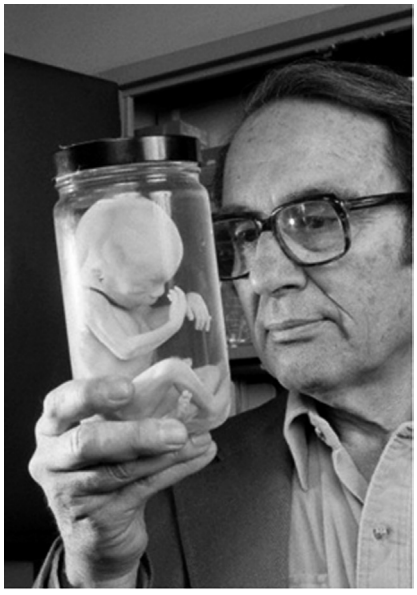


Fig. 1 (Left). Clifford Grobstein (1916-1998). *Grobstein published a series of pivotal papers that established the phenomenon of epithelial-mesenchymal interaction as a principle of development.*

Fig. 2 (Right). Roberto Montesano. *Montesano at the University Medical Center of Geneva, Switzerland, has extensively investigated the mechanisms underlying the generation of branching epithelial tubules (tubulogenesis) in the development of different organs.*

differentiates into epithelia which organizes themselves into proximal tubes and which join the distal tubules of the arborizing ureter, while the remainder provides the cellular matrix in which these tubules are embedded (Saxen, 1987). Reciprocal inductive interactions occur between the epithelium of the ureter and the adjacent mesenchyme (Grobstein, 1955, Saxen, 1970).

Grobstein (1955), (1956) cultured *in vitro* the ureteric epithelium and the adjacent mesenchyme alone or together, and demonstrated that the ureteric epithelium did not branch in the absence of the mesenchyme, while when they were cultured together, the epithelium branched and the nephrons formed regularly. Aufderheide *et al.,* (1987) showed that the incipient epithelium induced the expression of tenascin in the adjacent mesenchyme, and Montesano *et al.,* (1991) (Fig. 2) demonstrated that scatter factor/hepatocyte growth factor (HGF) induced the growth and branching of kidney epithelial cells.

More recently it has been demonstrated that the signal from the mesenchyme is glial-derived neurotrophic factor (GDNF) while its receptor RET is expressed in the ureteric bud (Shakya *et al.*, 2005). Mice with either the GDNF or RET gene knocked out form no kidney. If a GDNF slow-release bead is placed on a culture of nephrogenic mesenchyme from these embryos, then branching of the duct is restored in the GDNF knock out, which lacks the factor, but not in the RET knockout, which lacks the capacity to respond to it.

Reciprocal interactions of developing lung tissues

The experiments of Rudnick (1933) with grafts of chick lung strongly suggested that budding of the bronchial tree does not take place when the epithelium is deprived of its investing mesenchyme and she concluded that factors necessary for the production of orderly branching of the endodermal bud lie within the surrounding mesenchyme. Loffredo Sampaolo and Sampaolo (1961) cultivating chick and rabbit lung on a defined medium, discovered that removal of the mesenchyme from the right lung interrupts the process of epithelial branching. The unaltered left lung, adjoining, continues to branch normally. Dameron (1961) demonstrated that the epithelium of fetal lung, isolated in vitro, is incapable of morphogenesis. When the epithelium is recombined with pulmonary mesenchyme, development resumes. Using short-term cultures of cells dissociated from embryonic lung, Grover (1961a) found that when the medium is seeded, the cells begin to re-aggregate into one mass. Moreover, the effectiveness of both dissociation and re-aggregation decreased with increasing age (Grover, 1961b).

Mesenchyme, separated from fetal mouse lung and placed on plasma clots at some distances from the bare tracheobronchial tree, migrate toward the epithelium and arrange itself about the epithelium. Following re-association, epithelial branching proceeds and this process is maximally inhibited after irradiation of both components (Alescio *et al.*, 1963). Alescio and Cassini (1962 a,b) demonstrated that if a section of mesenchyme from the tracheal bud is removed and replaced by mesenchyme taken from a bronchial bud, and if the grafted lungs is cultivated in vitro, a supernumerary bud grows out from the epithelium beneath the grafting site. Normally, the trachea produces no extra branches.

When the epithelium of the new-forming was covered with the tracheal mesenchyme, it did not branch regularly (Wessells, 1970), and the epithelial lung buds can be induced to form also gastric glands, villi epithelia or hepatic cords, in the presence of the corresponding mesenchyme (Deuchar, 1975).

The composition of the extracellular glycosaminoglycans (GAGs) varies during different phases of lung development and influence branching and differentiation of lung epithelium (Becchetti *et al.*, 1988, Shannon, 1994).

More recently, it has been demonstrated that the branching morphogenesis of the developing lungs involves a lateral inhibition-type system whereby new tips produce fibroblast growth factor-10 (FGF-10) and suppress the formation of other tips in their immediate neighborhood (Volckaert and De Langhe, 2014).

Reciprocal interactions of developing limb tissues

The limb rudiment is initially specified as a territory in the mesoderm covered by an ectodermal epithelium. The mesenchyme is characterized by the presence of highly proliferating cells, named the progress zone, covered by a thick epithelia layer, named the apical ectodermal ridge (AER), the major signaling center for the developing limb.

In the 1960s, much experimental work has been directed to the study of the ectoderm-mesoderm interrelations in limb morphogenesis in the avian embryo. Two different hypothesis have been formulated. In both the main importance is attributed to the mesoderm of the site of the primary potencies for limb development.

One group of Authors (Zwilling, Saunders, Hampé, Tschumi, Milaire, Goetinck, and Abbott) considered the thickened portion

of the AER as a structure endowed with a mesoderm-dependent inductor activity (Saunders, 1948, Saunders and Reuss, 1974, Zwilling, 1956a, Zwilling, 1956b). The other group [Amprino (Fig. 3) and Camosso, Barasa, Belland and co-workers, Koeche] denied the inductor role of the AER, and attributed the major formative role to the mesoderm instead (Amprino, 1965, Kieny, 1960).

AER maintains the mesenchyme in a proliferating state (preventing it from form cartilage) that enables the linear growth of the limb; maintains the expression of those molecules that generate the anterior-posterior axis; interacts with the proteins specifying the anterior-posterior and dorsal-ventral axis. AER formation requires bone morphogenetic protein (BMP) signaling and can be prevented in transgenic mice by expressing a dominant negative BMP receptor under the control of an epidermis-specific promoter.

The signal for limb bud formation comes from mesodermal cells, which secrete FGF-10, capable of initiating interactions between the ectoderm and mesoderm (Xu *et al.*, 1998, Yonei-Tamura *et al.*, 1999). FGF-10 induces the overlying ectoderm to form the AER. Moreover, FGF-10 induces the AER to synthesize and secrete FGF-8, which stimulates mitosis in the mesenchymal cells. The FGF-10 knockout mouse forms no limb buds.

Epithelial-mesenchymal interactions in experimental recombination among tissues from different animal species

In 1952, Harold S. Fleming, published "Homologous and Heterologous Intraocular Growth of Transplanted Tooth Germs" in which he detailed the transplant of tooth germs from different species embryos or fetuses into the anterior chamber of the eyes of anesthetized mice, rabbits, and guinea pigs.

A number of recombinations between vertebrate tissues associated with epidermal organs, including skin, feather, mammary gland, salivary gland, tooth organ, suggest that regional mesenchymal specificity is instructive for determination and differentiation of epithelial phenotypes. In epidermal organs mesenchyme becomes determined and differentiates into a unique phenotype, such as during tooth organogenesis and odontoblast differentiation.

Fig. 3. Rodolfo Amprino (1912-2007). *Amprino proposed that the apical ectodermal ridge arises simply from the accumulation of ectodermal cells at the apex of the limb bud, as a consequence of the distalward sliding of the dorsal and ventral ectodermal faces of the bud.*

Homospecific tissue recombinations allow to demonstrate the essential role of mesenchyme in epithelial growth, morphogenesis, and cytodifferentiation. Moreover, epithelial components may also intervene in the control of morphogenesis and differentiation of mesenchymal cells such as odontoblasts, chondroblasts, osteoblasts, and muscle cells.

Further development

It is now well established that epithelial-mesenchymal interactions are now considered to constitute the single most important mechanism regulating organ development in vertebrates. The production of transgenic mice with deficient gene function has led to the identification of molecules that are required for the development of specific organs, including FGF, Hedgehog, Wingless, transforming growth factor beta (TGF-β), activin, BMPs. BMP-4 causes bone formation, cell death, and in other instances specifies the epidermis, while BMP-7 is important in neural tube polarity and kidney development (Daniel *et al.*, 1989, Ritvos *et al.*, 1995). In spite of the wide variety of molecules involved, common molecular mechanisms appear to govern the development in different organ systems.

FGF and TGFβ families mimicked the effects of inductive signals as it has been confirmed by inhibition experiments by using dominant negative mutations of growth factor receptor (Slack, 1994).

The FGF gene family comprises nearly two dozen structurally related members. FGF-8 is especially important during limb development and lens induction. FGF-8 is usually made by the optic vesicle that contact the outer ectoderm of the head. After contact with the outer ectoderm occurs, FGF-8 gene expression becomes concentrated in the region of the presumptive neural retina (Vogel-Hopker *et al.*, 2000).

The proteins of the Hedgehog family induce boundaries between cells. Three homologues of *Drosophila* Hedgehog gene are recognizable in Vertebrate: sonic Hedgehog (shh), desert Hedgehog (dhh), and Indian Hedgehog (ihh) (McMahon and Bradley, 1990, Stern *et al.*, 1995).

Concluding remarks

The term epithelial-mesenchymal interaction is one of the most common used in developmental biology. In fact, the range of tissues that form as a result of the interaction between mesenchyme and the ectodermic and endodermic epithelia is wide. These interactions show almost two common features: they are sequential and coordinated and are reciprocal, occurring in both directions between the epithelial and mesenchymal tissues. Mesenchyme influences epithelial growth, induces specific patterns of ductal branching, specifies epithelial morphology and spatial organization, and activates specific patterns of epithelial cytodifferentiation and functional activity.

During normal development regulated by epithelial-mesenchymal interactions take place an invasive epithelial behavior which, differently from that occurs in cancer cells, is under spatial and temporal regulation. The existence of common molecules involved in the regulation of cancer and development, suggests "the possibility that understanding their function and mode of action during normal devel-

opment can provide insights into their abnormal ones." (Arias, 2001).

References

ALESCIO, T. and CASSINI, A. (1962a). Epithelio-mesenchymal interaction in the organogenesis of the embryonal lung of the mouse cultured in vitro. *Z Anat Entwicklungsgesch* 123: 369-396.

ALESCIO, T. and CASSINI, A. (1962b). Induction *in vitro* of tracheal buds by pulmonary mesenchyme grafted on tracheal epithelium. *J Exp Zool* 150: 83-94.

ALESCIO, T., CASSINI, A. and LADU, M. (1963). Ricerche sulla riassociazione *in vitro* dell'epitelio e del mesenchima del polmone embrionale di topo, dopo dissociazione triptica ed irradiazione con raggi gamma. *Arch Ital Anat Embriol* 68: 1-44.

AMPRINO, R. (1965). Aspects of limb morphogenesis in the chicken. In *Organogenesis*, (eds. R, DE HAAN and H, URSPRUNG). Holt, Rinehart and Winston, New York, pp. 225-281.

ARIAS, A.M. (2001). Epithelial mesenchymal interactions in cancer and development. *Cell* 105: 425-431.

AUFDERHEIDE, E., CHIQUET-EHRISMANN, R. and EKBLOM, P. (1987). Epithelial-mesenchymal interactions in the developing kidney lead to expression of tenascin in the mesenchyme. *J Cell Biol* 105: 599-608.

BECCHETTI, E., EVANGELISTI, R., STABELLINI, G., PAGLIARINI, A., DEL BORRELLO, E., CALASTRINI, C. and CARINCI, P. (1988). Developmental heterogeneity of mesenchymal glycosaminoglycans (GAG) distribution in chick embryo lung anlagen. *Am J Anat* 181: 33-42.

DAMERON, F. (1961). The influence of various mesenchyma on the differentiation of the pulmonary epithelium of the chick embryo in culture in vitro. *J Embryol Exp Morphol* 9: 628-633.

DANIEL, C.W., SILBERSTEIN, G.B., VAN HORN, K., STRICKLAND, P. and ROBINSON, S. (1989). TGF-beta 1-induced inhibition of mouse mammary ductal growth: developmental specificity and characterization. *Dev Biol* 135: 20-30.

DEUCHAR, E. (1975). *Cellular interactions in animal development*. Chapman & Hall, London.

EKBLOM, P., ALITALO, K., VAHERI, A., TIMPL, R. and SAXEN, L. (1980). Induction of a basement membrane glycoprotein in embryonic kidney: possible role of laminin in morphogenesis. *Proc Natl Acad Sci USA* 77: 485-489.

EKBLOM, P., LEHTONEN, E., SAXEN, L. and TIMPL, R. (1981). Shift in collagen type as an early response to induction of the metanephric mesenchyme. *J Cell Biol* 89: 276-283.

FLEMING, H.S. (1952). Homologous and heterologous intraocular growth of transplanted tooth germs. *J Dental Res* 31: 166-176.

GROBSTEIN, C. (1954). Tissue interaction in the morphogenesis of mouse embryonic rudiments in vitro. In *Aspects of Synthesis and Order in Growth*, (ed. RUDNICK, D.). Princeton University Press, pp. 223-256.

GROBSTEIN, C. (1955). Tissue disaggregation in relation to determination and stability of cell type. *Ann N Y Acad Sci* 60: 1095-1107.

GROBSTEIN, C. (1956). Trans-filter induction of tubules in mouse metanephrogenic mesenchyme. *Exp Cell Res* 10: 424-440.

GROBSTEIN, C. (1967). Mechanisms of organogenetic tissue interaction. *Natl Cancer Inst Monogr* 26: 279-299.

GROVER, J.W. (1961a). The enzymatic dissociation and reproducible reaggregation *in vitro* of 11-day embryonic chick lung. *Dev Biol* 3: 555-568.

GROVER, J.W. (1961b). The relation between the embryonic age of dissociated chick lung cells and their capacity for reaggregation and histogenesis in vitro. *Exp Cell Res* 24: 171-173.

GURDON, J.B., HARGER, P., MITCHELL, A. and LEMAIRE, P. (1994). Activin signalling and response to a morphogen gradient. *Nature* 371: 487-492.

GURDON, J.B., MITCHELL, A. and MAHONY, D. (1995). Direct and continuous assessment by cells of their position in a morphogen gradient. *Nature* 376: 520-521.

JONES, C.M., DALE, L., HOGAN, B.L., WRIGHT, C.V. and SMITH, J.C. (1996). Bone morphogenetic protein-4 (BMP-4) acts during gastrula stages to cause ventralization of *Xenopus* embryos. *Development* 122: 1545-1554.

KIENY, M. (1960). Inductive role of the mesoderm in the early differentiation of the limb bud in the chick embryo. *J Embryol Exp Morphol* 8: 457-467.

LOFFREDO SAMPAOLO, C. and SAMPAOLO, G. (1961). Indagini sperimentali sullo sviluppo del polmone embrionale (pollo e coniglio). *Quaderni di Anatomia Pratica* 17: 1-43.

MCMAHON, A.P. and BRADLEY, A. (1990). The Wnt-1 (int-1) proto-oncogene is required for development of a large region of the mouse brain. *Cell* 62: 1073-1085.

MONTESANO, R., SCHALLER, G. and ORCI, L. (1991). Induction of epithelial tubular morphogenesis *in vitro* by fibroblast-derived soluble factors. *Cell* 66: 697-711.

NOHNO, T., KAWAKAMI, Y., OHUCHI, H., FUJIWARA, A., YOSHIOKA, H. and NOJI, S. (1995). Involvement of the Sonic hedgehog gene in chick feather formation. *Biochem Biophys Res Commun* 206: 33-39.

REILLY, K.M. and MELTON, D.A. (1996). Short-range signaling by candidate morphogens of the TGF beta family and evidence for a relay mechanism of induction. *Cell* 86: 743-754.

RITVOS, O., TUURI, T., ERAMAA, M., SAINIO, K., HILDEN, K., SAXEN, L. and GILBERT, S.F. (1995). Activin disrupts epithelial branching morphogenesis in developing glandular organs of the mouse. *Mech Dev* 50: 229-245.

RUDNICK, D. (1933). Developmental capacities of the chick lung in chorioallantoic grafts. *J Exp Zool* 66: 125-154.

SAKAKURA, T. (1991). New aspects of stroma-parenchyma relations in mammary gland differentiation. *Int Rev Cytol* 125: 165-202.

SAUNDERS, J.W., JR. (1948). The proximo-distal sequence of origin of the parts of the chick wing and the role of the ectoderm. *J Exp Zool* 108: 363-403.

SAUNDERS, J.W., JR. and REUSS, C. (1974). Inductive and axial properties of prospective wing-bud mesoderm in the chick embryo. *Dev Biol* 38: 41-50.

SAXEN, L. (1970). Failure to demonstrate tubule induction in a heterologous mesenchyme. *Dev Biol* 23: 511-523.

SAXEN, L. (1987). *Organogenesis of the kidney*. Cambridge University Press.

SAXEN, L., LEHTONEN, E., KARKINEN-JAASKELAINEN, M., NORDLING, S. and WARTIOVAARA, J. (1976). Are morphogenetic tissue interactions mediated by transmissible signal substances or through cell contacts? *Nature* 259: 662-663.

SHAKYA, R., WATANABE, T. and COSTANTINI, F. (2005). The role of GDNF/Ret signaling in ureteric bud cell fate and branching morphogenesis. *Dev Cell* 8: 65-74.

SHANNON, J.M. (1994). Induction of alveolar type II cell differentiation in fetal tracheal epithelium by grafted distal lung mesenchyme. *Dev Biol* 166: 600-614.

SLACK, J.M. (1994). Inducing factors in *Xenopus* early embryos. *Curr Biol* 4: 116-126.

SLAVKIN, H.C. and BRINGAS, P., JR. (1976). Epithelial-mesenchyme interactions during odontogenesis. IV. Morphological evidence for direct heterotypic cell-cell contacts. *Dev Biol* 50: 428-442.

STERN, H.M., BROWN, A.M. and HAUSCHKA, S.D. (1995). Myogenesis in paraxial mesoderm: preferential induction by dorsal neural tube and by cells expressing Wnt-1. *Development* 121: 3675-3686.

TING-BERRETH, S.A. and CHUONG, C.M. (1996). Sonic Hedgehog in feather morphogenesis: induction of mesenchymal condensation and association with cell death. *Dev Dyn* 207: 157-170.

VOGEL-HOPKER, A., MOMOSE, T., ROHRER, H., YASUDA, K., ISHIHARA, L. and RAPAPORT, D.H. (2000). Multiple functions of fibroblast growth factor-8 (FGF-8) in chick eye development. *Mech Dev* 94: 25-36.

VOLCKAERT, T. and DE LANGHE, S. (2014). Lung epithelial stem cells and their niches: Fgf10 takes center stage. *Fibrogen Tissue Rep* 7: 8.

WESSELLS, N.K. (1970). Mammalian lung development: interactions in formation and morphogenesis of tracheal buds. *J Exp Zool* 175: 455-466.

XU, X., WEINSTEIN, M., LI, C., NASKI, M., COHEN, R.I., ORNITZ, D.M., LEDER, P. and DENG, C. (1998). Fibroblast growth factor receptor 2 (FGFR2)-mediated reciprocal regulation loop between FGF8 and FGF10 is essential for limb induction. *Development* 125: 753-765.

YONEI-TAMURA, S., ENDO, T., YAJIMA, H., OHUCHI, H., IDE, H. and TAMURA, K. (1999). FGF7 and FGF10 directly induce the apical ectodermal ridge in chick embryos. *Dev Biol* 211: 133-143.

ZWILLING, E. (1956a). Intercation between limb bud ectoderm and mesoderm in the chick embryo. I. axis establishment. *J Exp Zool* 132: 157-171.

ZWILLING, E. (1956b). Intercation between limb bud ectoderm and mesoderm in the chick embryo. II. Experimental lim duplication. *J Exp Zool* 132: 173-187.

Further Related Reading, published previously in the *Int. J. Dev. Biol.*

Differential expression of angiogenic and anti-angiogenic molecules in the chick embryo chorioallantoic membrane and selected organs during embryonic development
Christian Marinaccio, Beatrice Nico and Domenico Ribatti
Int. J. Dev. Biol. (2013) 57: 907-916
http://dx.doi.org/10.1387/ijdb.130317dr

Zebrafish enhancer trap line recapitulates embryonic *aquaporin 1a* expression pattern in vascular endothelial cells
Kira Rehn, Kuan Shen Wong, Darius Balciunas and Saulius Sumanas
Int. J. Dev. Biol. (2011) 55: 613-618
http://dx.doi.org/10.1387/ijdb.103249kp

Zebrafish embryo, a tool to study tumor angiogenesis
Chiara Tobia, Giulia De Sena and Marco Presta
Int. J. Dev. Biol. (2011) 55: 505-509
http://dx.doi.org/10.1387/ijdb.103238ct

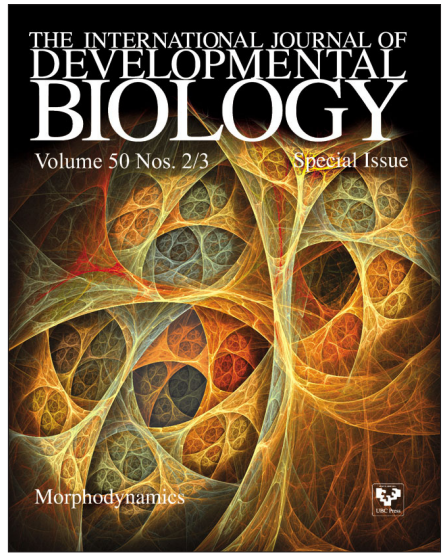
The use of the orthotopic model to validate antivascular therapies for cancer
Monica Loi, Daniela Di Paolo, Pamela Becherini, Alessia Zorzoli, Patrizia Perri, Roberta Carosio, Michele Cilli, Domenico Ribatti, Chiara Brignole, Gabriella Pagnan, Mirco Ponzoni and Fabio Pastorino
Int. J. Dev. Biol. (2011) 55: 547-555
http://dx.doi.org/10.1387/ijdb.103230ml

Tumor blood vessel visualization
Jeannine Missbach-Guentner, Julia Hunia and Frauke Alves
Int. J. Dev. Biol. (2011) 55: 535-546
http://dx.doi.org/10.1387/ijdb.103229jm

Paracrine regulation of angiogenesis by different cell types in the aorta ring model
Roberto F. Nicosia, Penelope Zorzi, Giovanni Ligresti, Ann Morishita and Alfred C. Aplin
Int. J. Dev. Biol. (2011) 55: 447-453
http://dx.doi.org/10.1387/ijdb.103222rn

A brief history of angiogenesis assays
Anca-Maria Cimpean, Domenico Ribatti and Marius Raica
Int. J. Dev. Biol. (2011) 55: 377-382
http://dx.doi.org/10.1387/ijdb.103215ac

The role of angiogenic growth factors in organogenesis
Enrico Crivellato
Int. J. Dev. Biol. (2011) 55: 365-375
http://dx.doi.org/10.1387/ijdb.103214ec



5 yr ISI Impact Factor (2011) = 2.959