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A New Component of the Fraser Complex

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Summary

In embryos, the Fraser Complex (FC) mediates epithelial-connective tissue interactions. Loss of expression of FC components leads to Fraser Syndrome (FS) in which cohesion of epithelial tissues and stroma is perturbed. Using zebrafish, Richardson et al (in this issue) identified the protein AMACO in the FC. We discuss the utility of zebrafish in determining FC functions and identifying FS targets.

The extracellular matrix (ECM) is a complex multiprotein network that not only supports tissue structure but also plays important roles in regulating cell and tissue development, differentiation, remodeling and repair. In some instances, ECM molecules associate into structures termed basement membranes (BMs), which are found in nearly all tissues (Yurchenco 2011). BMs in a diverse set of tissues exhibit many ultrastructural similarities, being composed of two layers termed the lamina lucida, an electron lucid zone lying immediately under the cells, and the laminin densa, an electron dense sheet-like array which sits over the connective tissue. However, composition of a BM is dictated by the cells that deposit its components and, hence, varies between tissues. Moreover, changes in BM composition take place during development. Such is the case for the BM underlying keratinocytes in skin. In adult skin, laminin-332 links to type VII collagen, a component of anchoring fibrils, which extend into the dermis (Yurchenco 2011). In contrast, type VII collagen is absent in the developing skin of the early embryo. Rather, a group of related proteins termed the Fraser Complex (FC) appears to substitute for type VII collagen in the developing embryo where they stabilize epithelial-mesenchymal interaction (Pavlakis et al. 2011).

The FC is composed of the Fras1/Frem family of ECM proteins (Pavlakis et al. 2011). Members of this family, including Fras1 and Frem1-3, possess 12 repeats of a domain with homology to the chondroitin sulfate proteoglycan (CSPG) motif in the NG2 protein and one or more Calx-β domains (Pavlakis et al. 2011). In the mouse, Fras1, Frem 1, and Frem2 are found in BMs primarily during embryogenesis, and they are present in small amounts in adult BMs, while Frem3 is present in BMs throughout development, persisting into adulthood (Pavlakis et al. 2011). Fras1/Frem proteins form a ternary complex and are believed to stabilize each other (Pavlakis et al. 2011). The importance of the complex in development is indicated by the finding that its loss in humans results in a disease termed

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Fraser Syndrome (FS), while its absence in the mouse induces blebbing or blister formation in the head region, over the eye or brain, and distally in the limbs (Pavlakis et al. 2011).

FS is a rare autosomal recessive congenital disorder characterized by cryptophthalmos, syndactyly, and abnormalities of the respiratory and urogenital tracts (Pavlakis et al. 2011). The incidence of FS is 0.43 per 100,000 live birth and 11.06 in 100,000 still births (Pavlakis et al. 2011). Mutations in Fras1 are detected in approximately half of the affected cases, with some rare individuals carrying mutations in either Frem2 or glutamate receptor interacting protein 1 (GRIP1), a trafficking protein involved in localizing Fras1/Frem proteins at the membrane (Pavlakis et al. 2011; Vogel et al. 2012). Since these mutations do not account for all patients with FS, searches for additional components of the FC and mutations that lead to FS have been mounted. One approach has been use of the zebrafish genetic model. Zebrafish express known components of the FC. Moreover, fin blistering during development can be used as an indicator of FS. In this regard, the hemicentin1 and furin genes have both been identified as FS candidate disease genes following genetic analyses in zebrafish (Carney et al. 2010). However, whether the protein products of these putative disease genes are bona fide FC awaits rigorous biochemical analysis. In contrast, in a new paper, Richardson et al. (in this issue) present evidence of a novel protein (AMACO) associated with FC proteins in fish and mice, and they demonstrate that AMACO can bind directly to Fras1.

AMACO is an ECM protein containing von Willebrand factor A (VWA) domains related to those in MAtrilins and COllagens, hence its name (Sengle et al 2003). Like FC proteins, AMACO localizes to the BMs of various tissues during development (Gebauer et al. 2009). Indeed, Richardson and her co-workers show that it co-localizes precisely with Fras1 (Richardson et al., in press). Moreover, these same authors present evidence that a fragment of AMACO containing its cysteine-rich domain, one of its EGF-like domains, and one VWA region directly interacts with the CSPG repeats in Fras1. In mice and zebrafish lacking Fras1, there is a concomitant loss of AMACO. Although AMACO deficiency has no obvious impact on zebrafish development, its loss exacerbates the fin blistering induced by Fras1 ablation (Richardson et al., in press). Based on these findings, one would assume that an AMACO mutation itself is unlikely to cause FS. Rather, as the authors speculate, AMACO mutations may mediate “a predisposition” for FS, possibly by destabilizing an already compromised FC containing mutant protein or missing one of its structural elements (Richardson et al., in press).

The lack of developmental defects in zebrafish deficient in AMACO likely indicates a compensatory mechanism when AMACO is missing from the embryo. The absence of AMACO close family members in the zebrafish genome suggests that if such compensation occurs then it is mediated by a distant relative or protein with similar properties capable of interacting with the FC. Of course, this raises questions as to what exactly AMACO and the FC do in the developing embryo. The presence of several VWA domains in AMACO implies that AMACO is involved in adhesion, migration, homing and signaling following ligand activation (Sengle et al. 2003). Interestingly, AMACO also contains an RGD motif close to its C-terminus allowing it to interact with integrins. Thus, it could induce signaling in those cells with which it interacts (Gebauer et al. 2009). The FC may also be more than a

structural matrix complex in BMs during development. Frem1 may facilitate α8β1 integrin binding to ECM through nephronectin assembly in the BM and regulate collagen deposition by binding platelet-derived growth factor C (PDGFC)(Kiyozumi et al. 2012; Wiradjaja et al. 2013). The latter induces signaling through the PDGFC receptor which regulates matrix remodeling. In addition, Fras1 contains von Willebrand C-like domains which also might allow it to bind and regulate growth factors (Pavlakis et al. 2011).

In summary, Richardson et al. (in this issue) have identified AMACO as a bona fide component of the FC and provide evidence that it modulates FC functions in vivo. Further analyses of the functions of both AMACO and the components of the FC are essential if we are to understand the pathology underlying FS. The zebrafish is an ideal genetic model to accomplish this goal. A number of studies have provided evidence that there is upregulation of FC proteins, including Fras1, Frem1 and AMACO, in some cancers (Gebauer et al. 2009). Although their function in tumors is unclear, we speculate that their expression and function is somehow mimicking what occurs during tissue development in the embryo, possibly by inducing matrix remodeling and signaling that promote metastasis. In this regard, it would be interesting to assess whether an upregulation of FC proteins occurs in an attempt to compensate for the lack of type VII collagen in the skin of patients afflicted with dystrophic epidermolysis bullosa (DEB), mirroring the substitution of FC proteins by type VII collagen in the developing integument (Pavlakis et al. 2011). If this is the case, then FC protein expression may contribute to the development of aggressive and invasive skin cancer afflicting DEB patients (South and O'Toole 2010).

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Clinical Implications

1. FC components are essential for BM functions in the developing embryo.
2. Mutations in FC components result in a number of features including skin coverage of the globes of the eye, cutaneous syndactyly and abnormal genitalia.
3. AMACO mutations may mediate a genetic predisposition to FC in certain individuals.