

P045 The elongated and modular organization of fibronectin revisited by the structure of its 45kDa gelatin binding domain
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Fibronectin (Fn) is a modular extracellular matrix protein involved in cell adhesion, cell motility, wound healing and maintenance of cell morphology. Fn and some of its isoforms play a significant role in cancer progression by increasing the migration and proliferation of human carcinoma cells. Fn is schematically depicted as a “string of beads” composed of multiple repeats of three distinct modules: F_I, F_{II} and F_{III}. Association of these modules creates fragments able to interact with different constituents of the extracellular matrix. Here, we present the 2.4 Å resolution crystal structure of its 45 kDa gelatin binding domain (6F_I-1F_{II}-2F_{II}-7F_I-8F_I-9F_I) which also corresponds to the C-terminal half of the migration stimulating factor, a protein expressed in human breast cancers. This crystal structure of the GBD from human Fn completely modifies the current perception of the organisation of this large glycoprotein at the cell surface. The association of this fragment as zinc-mediated compact homodimers in solution combined with the fact that 7F_I, 8F_I and 9F_I form a single structural subdomain, invalidates the current “pearls on string” model. In addition, the 8F_I fold deviates completely from other F_Is with which it shares up to 40% sequence identity. This study warrants against the naïve view of multimodular proteins as simple assemblages of modules. As shown here, even the fold of a module can be context dependent. The role of Zn²⁺ in the biological functions, dynamics and structure of both Fn and MSF should be further investigated.