Trefoil Factor Family (TFF) Peptides

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Contributor: Werner Hoffmann

Trefoil factor family (TFF) peptides mainly consist of characteristic TFF domains, which contain about 40 amino acid residues, including 6 conserved cysteine residues. TFF peptides possess a single (mammalian TFF1 and TFF3), two (mammalian TFF2, Xenopus laevis xP2) or four TFF domains (X. laevis xP4). They exhibit lectin activities and are characteristic exocrine products of the mucous epithelia. Here, they play different roles for mucosal protection and the innate immune defense: TFF1 is a gastric tumor suppressor; TFF2 builds a lectin complex with the mucin MUC6, physically stabilizing the inner gastric mucus layer; and TFF3 forms a disulfide-linked heterodimer with IgG Fc binding protein (FCGBP), probably preventing the infiltration of microorganisms. Minor amounts of TFF peptides are endocrine products of the immune and nervous systems. Pathologically, TFF peptides are linked to inflammation. There are increasing indications that TFF peptides can antagonize cytokine receptors, such as receptors for IL-1β, IL-6, and TNFα (thereby acting as anti-inflammatory peptides). TFF peptides can probably also activate a variety of receptors, such as CXCR4. The TFF domain is a unique shuffled module which is also present in a number of mosaic proteins, such as zona pellucida proteins, sugar degrading enzymes and frog skin mucins. Here, their function seems to be defined by a lectin activity, which might even allow a role in fertilization.

Keywords: TFF-domain ; lectin ; inflammation ; cytokine receptors ; innate immune defense ; gastric cancer ; re-active oxygen species ; macrophages

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Members of the trefoil factor family, i.e., mammalian TFF1, TFF2, and TFF3, are primarily considered secretory peptides involved in mucosal protection and defense (reviews: [1][2][3][4][5][6][7][8][9][10][11][12][13][14]). Furthermore, they are synthesized in the immune and nervous systems, and probably also blood vessels. They share a common cysteine-rich structural motif, the TFF domain (formerly: trefoil domain [1], P-domain [3]).

Historically, human TFF1 (formerly “pS2”) was discovered in 1982 as an estrogen responsive transcript [15]. TFF2 (formerly “pancreatic spasmolytic polypeptide”) was detected independently at the same time [16], and a first sequence appeared in 1985. The similarity of TFF1 and TFF2 was only recognized in 1988 when TFF domains were detected in the frog integumentary mucin FIM-A.1 (formerly “spasmolysin”) [17]. TFF3 (formerly “intestinal trefoil factor” or “hP1.B”) was described in 1991 in the rat [18] and in 1993 in humans [19][20]. Thus, the discovery was a result of four independent groups working in different fields (review: [21]). The present nomenclature is based upon an agreement reached at the Conférence Philippe Laudat in Aix-les-Bains in 1996 in order to avoid the single term “trefoil” because of its manifold meanings [22].

Thus far, TFF peptides have been characterized from amphibia to mammals. TFF modules already arose before amphibian evolution, i.e., in a tunicate and a nematode [21][23]). Furthermore, there is a number of mosaic proteins known which contain TFF domains, such as the human zona pellucida proteins ZP1 and ZPB, the sugar-degrading enzymes sucrose-isomaltase, α-glucosidase, and maltase-glucoamylase, the frog skin proteins APEG, “βγ-crystallin and trefoil factor” (βγ-CAT), and the frog integumentary mucins FIM-A.1 and FIM-C.1 (reviews: [12][21]).

Within the last four decades, our understanding concerning the biosynthesis and function of these peptides changed dramatically and only within the last years has a somewhat clearer picture emerged.

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