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REVIEW ARTICLE

Transglutaminases and receptor tyrosine kinases

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Abstract Transglutaminases are confounding enzymes which are known to play key roles in various cellular processes. In this paper, we aim to bring together several pieces of evidence from published research and literature that suggest a potentially vital role for transglutaminases in receptor tyrosine kinases (RTK) signalling. We cite literature that confirms and suggests the formation of integrin:RTK:transglutaminase complexes and explores the occurrence and functionality of these complexes in a large fraction of the RTK family.

Keywords Transglutaminases · Integrins · Extracellular matrix · Receptor tyrosine kinases · Tissue transglutaminase · Fibronectin

Transglutaminases

Transglutaminases (TGases) are a family of structurally and functionally related Ca^{2+}-dependent enzymes that catalyse the formation of γ-glutamyl isopeptide bonds in proteins by transamidation of specific glutamine residues (Lorand and Graham 2003). In addition to their role in protein cross-linking, TGases are also known to catalyse deamidation, amine incorporation, esterification and phosphorylation of particular substrates and the slow hydrolysis of previously formed isopeptide bonds; elaborated in Lorand and Graham (2003). Although the broader physiological roles of TGases still remain unclear, their ability to cross-link extracellular matrix (ECM) proteins such as fibronectin (FN) (LeMosy et al. 1992), vitronectin (VN) (Sane et al. 1988), several collagens (Bowness et al. 1987; Kleman et al. 1995), laminin-nidogen complexes (Aeschlimann and Paulsson. 1991) and osteopontin (Kaartinen et al. 1997) are very well documented.

TG2 or tissue TG, the most carefully studied member of the family, is found and is active in both the cytoplasmic and the extracellular spaces (Fesus and Piacentini 2002). It associates with a wide range of integrins in both contexts: forming 1:1 complexes with the extracellular domain of the β1, β3 and β5 integrin subunits (Akimov et al. 2000; Zemskov et al. 2006), and binding the GFFKR sequence in the α_{IIb}, α_5 and α_v integrins (Kang et al. 2004), a motif that is strictly conserved in 13 of the 18 human α integrin subunits. Integrins are a family of heterodimeric transmembrane adhesion receptors that mediate cell-ECM adhesion by simultaneously binding ECM proteins outside the cell, clustering, and establishing linkage to the actin cytoskeleton inside the cell (Bokel and Brown 2002). TG2 has been shown to bind $\alpha 5\beta 1$ integrin and FN via two distinct domains which, subsequently allows the formation of ternary complexes in the ECM, including TG2-FN-integrin (Akimov and Belkin 2001; Akimov et al. 2000).

Integrins and receptor tyrosine kinases

Integrins have been found to play an important part in mediating cell-signalling events by regulating the binding of growth factors or cytokines to growth factor receptors, including a large number of RTKs (Legate et al. 2009). RTKs are a large family of single-pass transmembrane

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receptors wherein the binding of their respective ligands promotes the autophosphorylation of their cytoplasmic domains and initiates subsequent events that play key roles in most metazoan cellular processes (Robinson et al. 2000). Receptors from this family are of key interest in the investigation of phenomena such as developmental processes (Holder and Klein 1999), stem cell growth and differentiation (Arai et al. 2004), tissue maintenance and wound healing (Upton et al. 2008), diabetes (Robinson et al. 2000) and the pathogenesis, drug resistance and metastasis of cancers (Hollier et al. 2008; Kashyap et al. 2011; Samani et al. 2007). Activities of several RTKs have been demonstrated to be modulated by ligand binding to integrins (Somanath et al. 2009). Ligand occupancy of integrin receptors triggers integrin clustering and its association with the cytoskeleton. The close association between integrins and growth factor receptor complexes, demonstrated as clustering of RTKs within a few hundred nanometres of the integrins, has been most recently and comprehensively demonstrated using a new technique dubbed enzyme-mediated activation of radical source (EMARS) (Kotani et al. 2008). The $\alpha v\beta 3$ integrin has been reported to directly associate with several RTK family members, such as the platelet-derived growth factor receptor (PDGFR) (Schneller et al. 1997), vascular endothelial growth factor receptor (VEGFR) (Somanath et al. 2009), and the insulin-like growth factor-I receptor (IGF1R) (Clemmons and Maile. 2005). Similarly, the epidermal growth factor receptor (EGFR) has been shown to directly associate with $\alpha v\beta 1$ and $\alpha v\beta 4$ integrins (Falcioni et al. 1997). The association between integrins and growth factor receptors can lead to partial activation of the growth factor receptor, subsequently leading to faster downstream responses on ligand occupancy (Moro et al. 1998). Taking into consideration that RTKs cluster around the same integrins that TGs bind, it is possible that integrin-bound TGs affect RTKs and their signalling processes.

Established direct TG:integrin:RTK associations

The first evidence of a direct TG-mediated interaction between an RTK and an integrin came from the observation that factor XIIIa activates the VEGFR2 in a growth factor independent fashion by cross-linking the receptor to the $\alpha v\beta 3$ integrin and enhancing vascular endothelial cell migration, proliferation and survival (Dardik et al. 2005). In a follow-up study (Dardik and Inbal 2006), it was demonstrated that cytoplasmic TG2 also interacts with VEGFR-2, mediating VEGF-stimulated translocation of the receptor to the cell nucleus and down regulating the migratory effects of the growth factor. This establishes the underlying fact that there is a close association between the TGases and VEGFR.

The two platelet-derived growth factor receptors, PDGFRα and -β are close relatives of the VEGFR family, and share a similar extracellular domain structure. It is perhaps not surprising then, that a recent study demonstrated an association between PDGFRα and -β, TG2 and the $\beta 1$ integrin (Zemskov et al. 2009). TG2 binds the extracellular portion of either PDGFRα or -β, stimulating clustering of receptors with the $\beta 1$ integrins and enhancing receptor turnover, mitosis and migration (Zemskov et al. 2009).

An earlier study (Schneller et al. 1997) indicated that the PDGFR also interacts with the $\alpha v\beta 3$ integrin where ligand-dependent co-immunoprecipitation of $\alpha v\beta 3$, and a highly phosphorylated sub-fraction of PDGFR-β was observed. Moreover, the effects of PDGF on downstream signalling were significantly enhanced when cells were plated on the $\alpha v\beta 3$ ligand VN, rather than on the non-$\alpha v\beta 3$ ligand collagen I. Whether TGases play a role in the PDGFR-$\alpha v\beta 3$ interaction is an open question; given the parallels with the VEGFR2 it seems reasonable to consider that an interaction between PDGFR and the $\alpha v\beta 3$ integrin is indeed plausible.

RTKs for which RTK-integrin and RTK-TG interactions have been separately established

Cross-talk between the EGFR and various TG2-binding integrins, in both an EGF-independent (Moro et al. 1998) and EGF-dependent (Ricono et al. 2009) fashion, is a well established phenomenon. Interactions between TG2 and EGFR are similarly, yet separately, well established. Depending on the circumstances, stimulation of EGFR may inhibit (Antonyak et al. 2003) or enhance (Antonyak et al. 2004) TG2 expression. Similarly, TG2 has been documented to influence EGF signalling (Maruko et al. 2009; Toth et al. 2009); research demonstrating TG2's inhibitory effect on EGF signalling has additionally established that the extracellular domain of EGFR is a TG2 substrate (Maruko et al. 2009).

Members of the Ephs, the largest family of RTKs, display both positive and negative interactions with integrins under various circumstances (Alford et al. 2007). The ligands for these receptors, the ephrins, exist variously as transmembrane or soluble proteins. Soluble ephrin A1 and A5 are cross-linked into oligomers by TG2 in vitro; these complexes stimulate enhanced activation of EphA1 and -A4 compared to the monomeric species (Alford et al. 2007).

It has been conclusively demonstrated by our group and others that the IGF1R cooperates with certain integrins in its signalling (Doerr and Jones 1996; Goel et al. 2005; Hollier et al. 2008; Kricker et al. 2003; Maile et al. 2006; Upton et al. 2008; Van Lonkhuyzen et al. 2007). IGF1R is known to colocalize with $\beta 1$ integrins (Kiely et al. 2006; Kotani et al. 2008). Our research has shown that

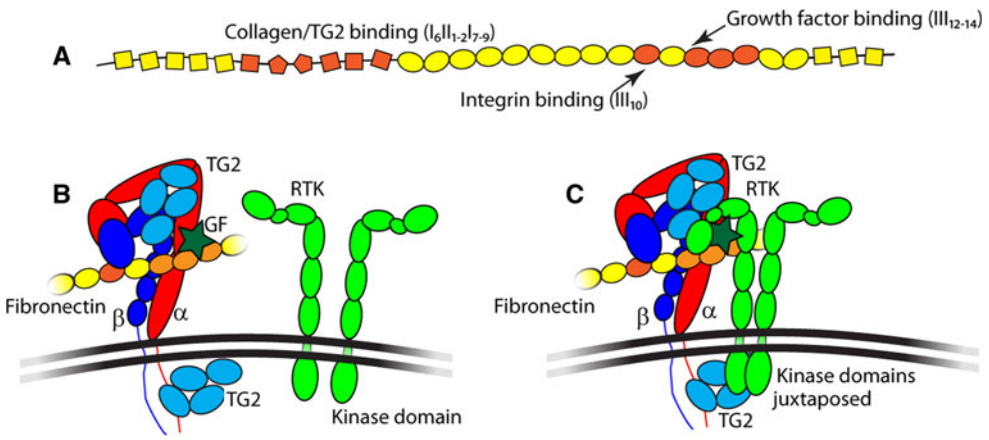

Fig. 1 FN, a key ECM protein, binds TG2, integrins, and a wide range of RTK-binding growth factors. **a** Schematic of the FN domain structure, highlighting key binding sites. FN binds TG2 within the 6-domain collagen binding region near its *N*-terminus, while integrin and growth factor binding sites are clustered near the *C*-terminus of the protein. **b** Binding to the $\alpha 5\beta 1$ integrin brings the growth factor binding region into juxtaposition with the $\beta 1$ integrin and hence, presumably, integrin-bound TG2. The large distance from the TG2 binding region suggests that TG2 binds a second FN chain, consistent with its role in FN fibrillogenesis; this has been omitted for clarity. An additional TG2 molecule may be found in complex with the GFFKR motif on the cytoplasmic tail of the alpha integrin. **c** Binding of an RTK to a FN-bound growth factor thus presented, necessarily brings both extra- and intracellular domains of the RTK into close proximity with integrin-bound TG2

noncovalent complexes of vitronectin, IGF binding proteins (IGFBPs) and IGF-I, or vitronectin-IGF-I chimeric analogues, can stimulate cell migration to a far greater extent than vitronectin or IGF-I alone (Hollier et al. 2008; Kricker et al. 2003; Van Lonkhuyzen et al. 2007). This strongly suggests that the same is true of the vitronectin-binding $\alpha v\beta 1$, -3 and -5 integrins. Direct insulin-dependent interaction of IR and IRS-1 (insulin receptor substrate 1) with the $\alpha v\beta 3$ integrin has also been demonstrated (Schneller et al. 1997; Vuori and Ruoslahti 1994). That these integrins are known to associate with TG2 at the cell surface (Fesus and Piacentini 2002) is certainly suggestive of the formation of a similar integrin:TG:receptor complex as has been observed for the VEGFR2 and PDGFR.

Tying it all together: ECM proteins present RTK ligands to integrin-bound TG2

As mentioned earlier, a substantial amount of work by our laboratory and others has demonstrated that VN, which binds EGF, bFGF, IGF-II and, via the IGFBPs, IGF-I, potently enhances the signalling of these growth factors compared to their free form via co-activation of their RTKs, VN- and the TG2-binding integrins such as $\alpha v\beta 1$, $\beta 3$ and $\beta 5$ (Doerr and Jones 1996; Goel et al. 2005; Hollier et al. 2008; Kricker et al. 2003; Maile et al. 2006; Upton et al. 2008; Van Lonkhuyzen et al. 2007). Such complexes, when bound to the integrin, bring the complexed growth factor into direct proximity to the integrin. The tertiary structure of FN is relatively well resolved compared to VN, and it has been recently shown that the 12th to 14th type-III domains of FN form an extremely promiscuous growth factor binding region, binding most members of the PDGF, VEGF and bFGF families as well as (via IGFBPs) IGF-I, but not EGF (Martino and Hubbell 2010). It can also be readily shown via existing crystal structures that when FN is bound to the integrin via its RGD sequence, the growth factor binding region must lie directly adjacent to the TG2-binding β integrin (Fig. 1). Once we consider all documented pairwise associations between integrins, TG2, FN (or VN), growth factors and RTKs, association of a growth factor thus bound with its cognate RTK is theoretically capable of bringing both intra- and extracellular domains of the RTK into close proximity with integrin-associated TG2.

A relationship between RTKs, integrins and TGases may be common to the entire RTK family

Direct, ternary association between RTKs, integrins and TGases has thus been demonstrated for three members of the RTK family, while circumstantial evidence in the form of colocalisation with integrins, and separate functional interactions with integrins and TGases exists for at least four more. It is instructive to consider the relationship between these receptors in the context of the RTK family tree (constructed according to the methods of Robinson et al. (2000) (Fig. 2). If we consider only those receptors for which a RTK:TG:integrin complex has been definitively demonstrated, the number of implicated receptors is rather small (those highlighted in green). If, however, we consider the more general criteria of separate, documented

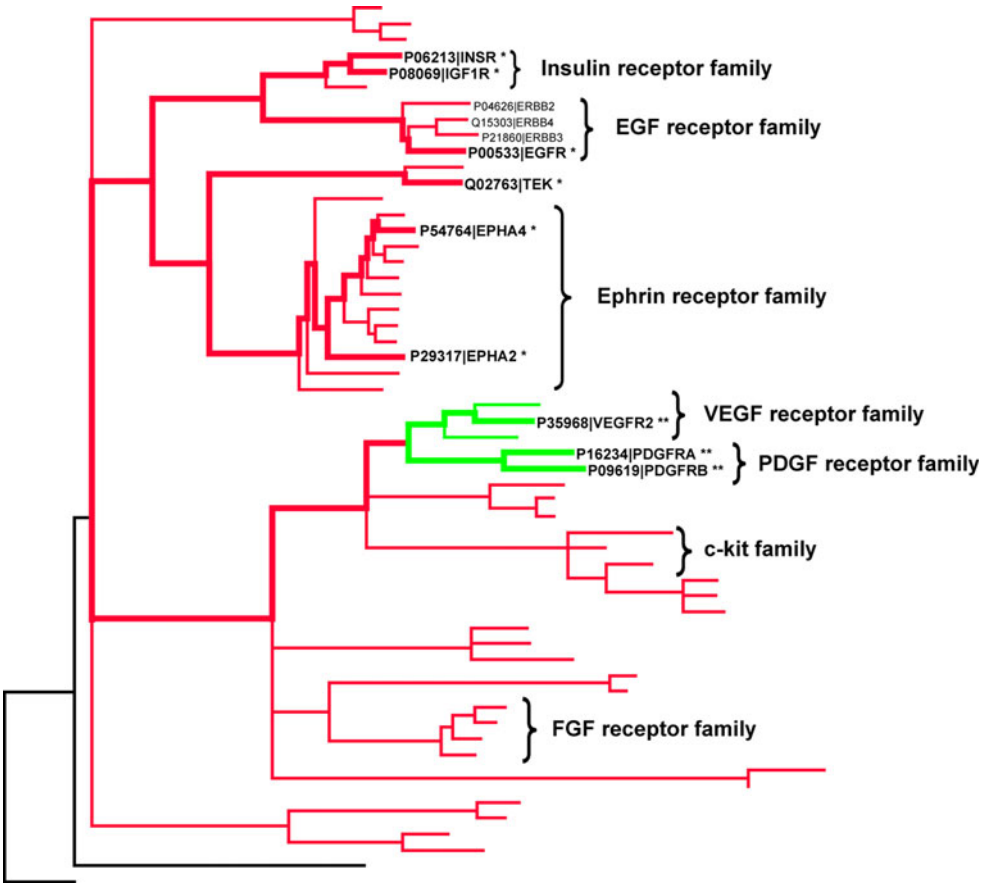

Fig. 2 A phylogenetic tree of the RTK family [adapted from Robinson et al. (2000) and annotated to indicate current knowledge regarding their associations with TGs. Each RTK is labelled with its UniProt accession number and gene name. *Asterisk* Separate, documented RTK:integrin and RTK:TGase interactions. *Double asterisks* Confirmed existence of an integrin:TGase:RTK complex

interactions with TGase and the TG2-binding integrins, the last common ancestor of the RTKs discussed in this review is in fact the last common ancestor of all but two of the human RTKs. We suggest that all members of the RTK family must therefore be at least tentatively considered to undergo similar interactions.

Conclusions

Given the current state of knowledge, expanding interest towards discovery of the relationship between RTKs and TGases will enable us to improve our understanding of the pattern of TG-mediated interactions under various conditions, and how this is disrupted in disease states. In keeping with this, TGases have been demonstrated to play key roles in a surprising array of apparently unrelated diseases, the most serious of which are cancers (Mehta et al. 2010), intracellular plaque-related neurodegenerative disorders (Jeitner et al. 2009) and autoimmune diseases (Dieterich et al. 2006).

Here we have outlined, how increasing evidence directs to how TGases and RTKs work together and this in turn raises possibilities of how this could act as a fundamental mediator of the eukaryotic signalling and trafficking system.

Acknowledgments Queensland University of Technology has filed a patent related to Transglutaminases and insulin-like growth factors. An inventorship audit is underway and all the authors of this paper may be deemed inventors. Tissue Therapies Ltd, a company spun out of Queensland University of Technology, has a license to commercialize this intellectual property. Z.U holds shares in and is a consultant for Tissue Therapies Ltd.

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