s1.m8.p10 **Structure of the integrin a2b1 binding collagen peptide.** Jonas Emsley,[a] Graham Knight[b] and Richard Farndale[b], [a]*Department of Biochemistry, University of Leicester, Leicester, UK, and* [b]*Department of Biochemistry, University of Cambridge, Cambridge, UK. E-mail: je14@le.ac.uk*

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We have determined the 1.8Å crystal structure of a triple helical integrin-binding collagen peptide (IBP) with sequence (Gly-Pro-Hyp)2-Gly-Phe-Hyp-Gly-Glu-Arg-(Gly-Pro-Hyp)3 [1]. The central GFOGER hexapeptide is recogised specifically by integrins α2β1, α1β1, α10β1, α11β1. These integrin/collagen interactions are implicated in a number of key physiological processes including cell adhesion, cell growth and differentiation and pathological states such as thrombosis and tumor metastasis. Comparison of the IBP structure with the previously determined structure of an identical collagen peptide in complex with the integrin α2-I domain (IBP^c) [2] allows the first detailed examination of collagen in a bound and an unbound state. The IBP structure shows a direct and a water mediated electrostatic interaction between Glu and Arg sidechains from adjacent strands but no intrastrand interactions. The interactions between IBP Glu and Arg sidechains are disrupted upon integrin binding. A comparison of IBP and IBP^c main chain conformation reveals the flexible nature of the triple helix backbone in the imino poor GFOGER region. The structure reveals this flexibility to be important to the integrin-collagen interaction and provides a possible explanation for the unique orientation of the three GFOGER strands observed in the integrin IBPc complex crystal structure.

[1] J. Emsley, G.C. Knight, R.W. Farndale, M.J. Barnes, (2004) Structure of the integrin a2b1 binding collagen peptide. *J. Mol. Biol* **335**, 1019-1028.

[2] J. Emsley, G.C. Knight, R.W. Farndale, M.J. Barnes, R.C., Liddington. (2000). Structural basis of collagen recognition by integrin a2b1. *Cell 100*, 47-56.

s1.m8.p11 **Structure and Signaling in the Epidermal Growth Factor Receptor Family.** TPJ Garrett[a], M-Z Lou[a], NM McKern[b], TE Adams[b], GO Lovrecz[b], EC Nice[c], AW Burgess[c], CW Ward[b], [a]*Walter and Eliza Hall Institute,* [b]*CSIRO Division of Health Science and Nutrition and* [c]*Ludwig Institute for Cancer Research, Parkville, Australia. E-mail: tgarrett@wehi.edu.au*

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Epidermal growth factor receptor (EGFR) is the cell surface receptor for small polypeptide cytokines such as EGF, and it stimulates cell proliferation and growth in a wide variety of epithelial tissues. Upon the binding ligand outside the cell, receptors dimerise into a novel 2:2 complex which then initiates intracellular signaling via cytoplasmic tyrosine kinase domains. The EGFR family contains three other receptors, erbB2 (neu or HER-2), erbB3 and erbB4, and these receptors can homo- and hetero-dimerise in a complex signaling network. Each member of the family has its own identity. For example, erbB2 has no ligand and the erbB3 kinase is inactive.

Medically, these receptors are key drug targets as increased or aberrant signaling via is characteristic of many cancers. For example, elevated levels of receptor or ligand have been observed in tumours of the brain, head and neck, lung, pancreas and colon. Furthermore, antibodies to EGFR have been shown to inhibit growth of epithelial cell lines in the laboratory and an antibody to erbB2 is currently in clinical trials as a therapy for breast cancer.

We have determined the structures of complexed and uncomplexed members of the EGFR family and these structures show that the receptors undergo a surprisingly large conformational change upon ligand binding. The structure of erbB2 also shows why it does not bind ligand and, indeed, why it does not need to. Unlike its relatives, it exists in a pre-activated state, ready to interact with potential partners. Closer comparisons of the receptor structures also reveal some more subtle differences. Twists and bends in the dimerisation domains of up to 40° hint that different ligands may have some fine specificity in receptor signaling.

Thus, structures of these receptor fragments provide substantial insight into the extracellular events leading to mitogenesis signaling via members of the EGFR family. However they also raise questions about the details of these events. A number of follow-up experiments have confirmed our initial hypotheses and results will be presented about a more detailed understanding of how EGFR family members interact.