LRP5, which could act as a decoy receptor. In three independent experiments they showed that these explants had lower bone mass than did explants cultured in media from cells expressing the wild-type, non-secreted form of LRP5. The authors additionally found that carriers of OPPG mutations also have reduced bone mass compared with non-carrier controls, suggesting that the activity of LRP5 is dosage sensitive.

These impressive results not only implicate LRP5 in the acquisition of bone mass, but they provide a clue as to how it does this. Given that LRP5 is expressed in several different tissues, one surprise is that the phenotypic effects of the mutation seem to appear only in the skeleton and the eye. This could mean that the functions of LRP5 are redundant or that it binds to other ligands too — questions that will need to be answered if pharmacological modulation of LRP5 is to be used in the fight against osteoporosis.

Alison Mitchell

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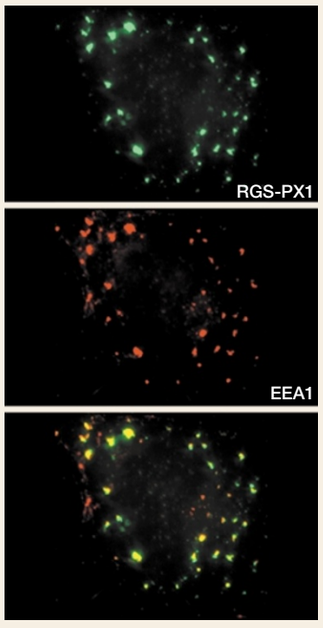
NIH osteoporosis and related bone diseases: http://www.osteo.org/

Warman laboratory: http://genetics.gene.cwru.edu/bone/



SIGNAL TRANSDUCTION

Chop and change

CD44 is an important cell-surface adhesion molecule. It is expressed in most human cell types and has been implicated in many physiological and pathological processes, such as cell migration and the regulation of tumour cell growth and metastasis. To meditate these processes, CD44 must be able to transduce numerous intracellular signals but how this occurs has remained unclear. Now, in *The Journal of Cell Biology*, Okamoto and co-workers report the identification of a novel CD44 signalling pathway.

It was previously shown that the extracellular ectodomain of CD44 can be proteolytically cleaved by membrane-associated metalloproteinases (MMPs) to produce soluble CD44 and membrane-bound CD44 ectodomain cleavage products. As this cleavage regulates the cell-migration function of CD44, Okamoto and colleagues investigated how proteolysis could affect other CD44 functions.

By inducing calcium influx or by using 12-*O*-tetradecanoylphorbol-13-acetate (TPA) treatment, the authors induced the activation of MMPs in human glioma cells. Using immunoblot analysis, they observed the expected CD44 ectodomain cleavage products, but, at a later timepoint, they also observed a smaller fragment of CD44, which corresponded to the intracellular domain (ICD). They showed that, after MMPs act to generate ectodomain cleavage products, further cleavage by intracellular proteases produces CD44ICD.

So what does CD44ICD do? In transiently transfected cells, Okamoto and co-workers showed that tagged CD44ICD is localized to the nucleus. This nuclear localization was also demonstrated for endogenous CD44ICD. Using a luciferase reporter, the authors showed that CD44ICD can enhance transcription that is mediated through the TPA-responsive element (TRE), and that CD44ICD translocation to the nucleus is essential for this enhancement. MMP inhibitors block CD44-dependent transcription enhancement and the enhancement is not observed when CD44 is mutated to remove the intracellular proteolytic cleavage site. The authors therefore concluded that sequential proteolytic cleavage of CD44 and release of CD44ICD is essential for CD44-dependent transcription enhancement.

Using GAL4 transactivation assays, the authors showed that CD44ICD alone is unlikely to act as a transcription factor. So, they tested the hypothesis that it affects other transcription factors — c-Fos and c-Jun — or transcriptional coactivators — CREB-binding protein (CBP) and p300 — involved in TRE-mediated transcription. CD44ICD did not affect GAL4–c-Fos- or GAL4–c-Jun-induced transcription from a GAL4-dependent promoter, but it did enhance transcription by GAL4–CBP and GAL4–p300. Whether the CD44ICD transactivation mediated through CBP/p300 occurs by a direct or indirect interaction remains to be determined.

To identify the endogenous gene targets of CD44ICD, the authors compared HeLa cells transfected with either a control plasmid or one encoding CD44ICD. The *CD44* gene contains TRE sequences in its promoter region, and Okamoto and co-workers found that CD44ICD induces *CD44* expression. They propose that this CD44ICD-induced *CD44* transcription promotes the rapid turnover of CD44 that is required for cell migration.

Signalling pathways are usually thought to involve interactions between cell-surface proteins and cytoplasmic proteins, which, in turn, regulate gene transcription. Here, however, Okamoto and colleagues have shown that CD44 bypasses a step in this pathway, as CD44ICD itself can activate gene transcription. In addition to identifying a novel CD44 signalling pathway, this paper has highlighted an important functional link between proteolytic processing of cell-surface adhesion molecules and transcriptional activation in the nucleus.

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