Researchers take a major step towards better diagnosis and treatment of osteoporosis

May 31 2014

A new target that may be critical for the treatment of osteoporosis, a disease which affects about 25% of post-menopausal women, has been discovered by a group of researchers in The Netherlands and in Germany. Professor Brunhilde Wirth, Head of the Institute of Human Genetics, University of Cologne, Germany, will tell the annual conference of the European Society of Human Genetics tomorrow (Sunday) that new studies in zebrafish and mice have shown that injection of human plastin 3 (PLS3) or related proteins in zebrafish where PLS3 action has been suppressed can replace its loss and repair the bone development anomalies associated with this deficiency. Furthermore, overexpression of human (PLS3) in normal mice had a significant impact on bone development and maintenance, making them more resistant to fractures.

The discovery that PLS3 mutations could cause osteoporosis was published last year in *The New England Journal of Medicine*. [1] The results came as a surprise to the researchers, since mutations in the PLS3 gene had not previously been known to be related to osteoporosis and fractures, or to play a role in bone formation. "In our most recent research, we started out by using zebrafish embryos in which PLS3 was knocked-out and studying their development at the three and five day-old stage," says Professor Wirth, "and we found that they had massive impairment of craniofacial skeletal development. However, this was fully restored when we added human PLS3. The same thing happened when we added two other proteins, actinin 1 and actinin 4, F-actin proteins[2] which are involved in 'bundling' or building the 'scaffolding'

for cells, and it seems that these proteins can compensate for the loss of PLS3. Thus we have been able to verify the essential role of actin in bone development and maintenance."

The subsequent mouse studies confirmed the findings in zebrafish, the researchers say, and open up possibilities for new treatments. They now intend to use PLS3 knock-out mice, where the PLS3 gene has been removed, in the search for the disease-causing mechanism involved. PLS3 is expressed in three different types of cells - osteocytes and osteoclasts, both involved in bone growth and remodelling, as well as in muscle cells. Using a transgenic mouse that overexpresses PLS3, they will also investigate whether this overexpression could be effective in other diseases involving in bone weakness.

"Since we know that about five percent of the human population expresses higher than normal levels of PLS3, we can hypothesise that these people may be protected against osteoporosis," says Professor Wirth. Once the researchers understand the exact disease-causing mechanism, it may be possible to translate the knowledge into therapy, they say. PLS3 overexpression is also protective against spinal muscular atrophy, the second most frequent autosomal recessive disorder in humans.[3] This implies that understanding the protective role of PLS3 is crucial in both disorders. "We are currently trying to unravel the whole protein network and, once we have understood the signalling pathways influencing PLS3 expression, we should be able to identify drugs or molecules that influence PLS3 expression or actin proteins," she says. Osteoporosis affects not only post-menopausal women, but also older men, and the condition currently causes more than 8.9 million fractures per year or an osteoporitic fracture every three seconds. Worldwide one in three women over 50 will experience fractures due to osteoporosis, as will one in five men. Currently, emphasis for sufferers is on the prevention of falls that can cause broken bones. Although bisphosphonates are useful in decreasing the risk of future fractures in

those who have already sustained an osteoporotic fracture, they are otherwise of little use.

"Osteoporosis poses an urgent health problem that is going to become more important as years go with the numbers of elderly people in the community continuing to increase," says Professor Wirth. "Although in itself it is not a fatal illness, large numbers of people die prematurely as a result of health complications following falls. We believe that our work has led to a better understanding of the condition and has pointed the way towards improved diagnosis and prevention, and, we hope, an effective treatment in the future."

More information: 1.N Engl J Med 2013; 369:1529-1536 DOI: 10.1056

2.F-actin is a multi-functional filamentous protein essential for regulating the mobility and contraction of cells.

3.An autosomal recessive disorder is one where two copies of an abnormal gene must be present in order to the disease or condition to develop.

Abstract no. C10.2

Provided by European Society of Human Genetics