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Perspective Article

Hylonome

Summary - Temporomandibular joint biology

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The temporomandibular joint (TMJ) is the site of articulation between the cranial base and mandible. Painful disorders affecting the TMJ are relatively common, affecting women of childbearing age more than men. These disorders can produce physical disfigurement, severe pain, and malnutrition.

The distinct features of the TMJ include its unique hinge and sliding movement, cellular and molecular architecture, physical properties and developmental regulation. The molecular and cellular composition of the fibrocartilages of the TMJ, and its material properties, are distinct from the articular cartilages of load-bearing joints of the appendicular skeleton. Previous studies have demonstrated that the fibrocartilages of the TMJ are less resilient to compressive loads than the hyaline cartilages of other articular joints. Finally, the recent observation that the TMJ is spared in patients suffering from the Hunter-Thompson chondrodysplasia, a congenital disorder resulting from a mutation of the cartilage-derived morphogenetic protein-1 gene, suggests that the molecular events that underlie the development of the TMJ differ from those involved in the development of other load-bearing joints.

Controversies regarding appropriate animal models used to study disease mechanisms affecting the TMJ have hampered progress in the field in previous years. These controversies are centered around the unique structural and mechanical features of the human TMJ. Most researchers believe that common TMJ diseases are initiated and sustained by abnormal joint mechanics. Therefore, many researchers insist that contemporary animal models are inadequate since they cannot accurately represent the mechanics of the human TMJ.

The use of primate models to study TMJ disorders has declined over recent years accounting for only 6% of animal research from 1998 to 2003. In recent years, rat models have become popular primarily among neuroscientists interested in joint nociception. The use of rabbits, pigs, sheep, and goats has also gained in popularity over the past decade. Interestingly, very little work has been done with the mouse. This is curious given the variety of transgenic mouse models available. It is likely that the mouse has not been used by many TMJ investigators due to technical difficulties imposed by the tiny size of the joint in this animal. Dr. Herring stressed that selection of an appropriate animal model used in TMJ research should be dependent upon the specific question being addressed by the investigator. Many of the existing animal models may be adequate for studies of basic mechanisms of disease. However, functional differences between species continue to be a persistent problem with all animal models. A perfect animal mimic of human TMJ mechanics is impossible. However, if one accepts this limitation then significant research can still be conducted using animal models that approximate function of the human TMJ, such as the pig model which has been extensively characterized.

A transgenic mouse overexpressing TNF-α demonstrates changes in the TMJ typical of a degenerative condition. In this model, pathologic changes are detected in the TMJ as early as six weeks of age. This observation suggests that TNF-α may be a key molecule involved in the genesis of some TMJ diseases. If so, anti-TNF-α therapies (e.g., etanercept, infliximab) may prove to be effective in the management of these diseases.

A novel potential therapeutic approach suggested by Dr. Puzas targets NFkB signaling. This signal transduction pathway is common to several cytokines, including TNF-α, believed to be involved in some degenerative arthritides. Dr. Puzas provided evidence that NFkB signaling could be inhibited by overexpression of IkB in a transgenic mouse. IkB interferes with nuclear translocation of NFkB required for signal transduction in this pathway.

Women of childbearing age appear to be particularly susceptible to some degenerative TMJ diseases. Previous studies have identified estrogen receptors in articular tissues of the TMJ raising the possibility that estrogens may govern susceptibility to disease. Estrogens may increase the sensitivity of cells in the TMJ to Relaxin H2, a 6 kDa hormone pre-

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viously known to mediate remodeling of the extracellular matrices of the female reproductive tissues and skin. Relaxin H2 induces collagenase and stromelysin expression by cells of the TMJ articular disk, but not synoviocytes, *in vitro*. This response is potentiated by estrogen. This work provides additional evidence of functional estrogen receptors expressed by cells of articular tissues of the TMJ. In addition, these data indicate at least one mechanism by which estrogens may predispose women to degenerative TMJ disease.

The session concluded with a brief discussion of existing clinical needs, particularly in reference to deficiencies of existing materials used to reconstruct diseased TMJs. The majority of patients who suffer from these debilitating diseases are young, and many require total joint reconstruction. In addition, the unique location of the TMJs, as well as their complex functional movements and load patterns, impose special requirements in the design of devices suitable for use in joint reconstruction. Contemporary TMJ prostheses, constructed primarily of titanium, do not afford normal joint movement and do not likely provide an adequate service life required for use in young adults. Novel tissue engineering approaches may offer substantial advantages over contemporary joint prostheses. However, significant preliminary work must be done to adequately characterize the articular tissues of the TMJ with respect to their molecular/cellular composition and material properties. In addition, accurate models depicting mechanical loads of the functioning TMJ must be developed to facilitate the design of a suitable prosthesis or tissue-like construct.