looking at the mechanisms for immune dysregulation in many of the connective tissue disorders, since the inflammatory processes involved in such chronic diseases as RA, SLE nephritis, WG, or scleroderma may have as much to do with loss of intrinsic modulating control mechanisms as with unabated production of autoantibodies of various specificities.

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REFERENCES

THERAPEUTIC IMPASSE IN OSTEOARTHRITIS

Osteoarthritis embodies a spectrum of disorders in which alterations in the chondrocyte and/or its microenvironment culminate in often irreparable cartilage destruction and compensatory bone remodelling. Primary (idiopathic) and secondary forms of disease are recognized, at times clinical, roentgenographic and pathologic features enabling distinct subsetting. Aberrant physiologic and pathologic changes have been largely attributed to a homeostatic imbalance created by accelerated catabolism and ineffectual matrix repair. Although predisposing factors vary from genetic connective tissue abnormalities and endocrine, metabolic and mechanical dysfunctions to aging and preceding inflammatory destructive disease, there are 'common pathway' mechanisms in the complex sequence of pathophysiologic events which can be therapeutically targeted.

Pathologic changes in cartilage appear in part to be induced by select cytokine, growth factor, connective tissue matrix constituent and biomechanical perturbances in chondrocyte metalloproteinase and oxygen metabolite expression. Immune and focal synovial tissue inflammatory responses to sequestered or structurally modified components of extracellular matrix
occurs in conjunction with quantitative and qualitative changes in collagen, proteoglycan and adhesive glycoprotein synthesis. Attrition is further afforded by abnormal forces creating mechanical wear.

In spite of considerable effort in the past three decades, we still know little of the "relative importance" of the basic pathophysiologic mechanisms presumed involved in disease induction and perpetuation. Problems are compounded because the physiology of normal cartilage metabolism is itself complex and poorly understood due to the potential influence of multiple factors originating both systemically and in an autocrine/paracrine manner within the local joint milieu. Cartilage structure and metabolism are to a large measure governed by the integrity of extracellular matrix. Essential nutrients are principally derived from synovial fluid, the diffusion of molecules governed by their size, charge and the pressure gradient established by cyclic joint loading. Water imbibition by polyanionic aggrecans species of proteoglycan provides viscoelasticity. A dominant type II collagen network contributes to structure, shape, strength and support. Adhesive glycoproteins and smaller molecular weight species of proteoglycan appear to function as growth factor 'reservoirs' and perhaps allow sequestration of molecules which modulate expression of proteinase activity. Clearly, preservation of the collagen scaffolding is critical for avoidance of irreversible pathologic change. One can thus appreciate the importance of therapeutic strategies that focus in a 'preventive' manner on early events in the pathophysiologic cascade.

Current pharmacologic options are limited and those in common use have not been shown to modify the basic disease process in humans. The interpretation of human and experimental animal studies which have addressed the potential efficacy of NSAIDs and heparinoid and other forms of "chondroprotective agents" is limited. Results have shown variability and the validity of some experimental designs could be questioned. There is uncertainty associated with the extrapolation of data obtained from in vitro "bench studies" or the induction of lesions in animals having no direct counterpart in humans. Far too often, promising agents developed to offset a given pathophysiologic event have been discarded because of lack of specificity, bioavailability or failure to attain effective therapeutic concentrations. It is important to recognize that reaction to a given agonist or antagonist often follows a concentration dependent response pattern and the desired effect achieved only within a relatively narrow dose range. Compromise in the integrity of the highly charged extracellular matrix of cartilage and its dense collagen network can clearly influence bioavailability and outcome.

Why have therapeutic options lagged so badly? Answers are clear. There remains a great deal yet to learn about the fundamental disease process. Although the most prevalent of the arthritides, until recently relatively little effort has been expended to this end. There are complex fundamental issues that require comprehensive cross-disciplinary analysis. What is of pathophysiologic importance at a given stage of disease? What factors dictate evolution? If presumptive mechanisms as listed are operative, i.e. cartilage literally lies within a caldron containing inducers and mediators which directly and indirectly upset chondrocyte metabolism, why is there focal tissue involvement? Why is disease relentlessly progressive in certain subsets yet remains stationary in others? Why are there apparent racial and sex differences in disease susceptibility? Following initial attempts to repair matrix, why does chondrocyte synthesis eventually fail to keep pace with attrition? Does this represent a preprogrammed event, i.e. do chondrocytes have only a finite response capacity? Why is there failure to restore biochemically and biomechanically normal matrix if the collagen network is compromised? Why are there individual differences in mounting repair responses? Why is there an apparent hormonal influence on disease expression in certain subsets and an apparent negative correlation with osteoporosis?

The adverse or protective intricate interplay between cytokines, growth factors and hormonal elements requires further dissection. Is it that governs the balance of expression of these factors and their indigenous regulators? Is it reasonable to develop a given cytokine or growth factor agonist or antagonist that may function only in a transient, restricted manner in a segment of the pathophysiologic cascade? Can growth factors be used in conjunction with chondrocyte/biopolymer transplantation to effect cartilage repair?

What strategies should be pursued to control cartilage matrix degrading proteinases produced by synovial tissue and chondrocytes? Should this be accomplished by inhibiting enzyme synthesis or by suppressing activity? Technical problems have restricted much of the current work in this area and results of limited clinical and animal studies have in general not been encouraging. Rational approaches can only be dictated by increasing our knowledge of the biochemistry and molecular biology of metalloproteinases and mechanisms which govern their transcription and activation. This would allow the exciting potential for development of therapies to precisely target a given regulatory site, enabling precise control of gene expression of enzyme or inhibitor. Beyond transcriptional mechanisms, the recognized heightened stability of metalloproteinase mRNA raises considerations for blockage using antisense oligonucleotides or specific therapies to enhance messenger decay.

The relevance of biophysical forces (hydrostatic pressure, fluid flow, streaming potentials, cell deformation) in directly modulating chondrocyte metabolism or its sensitivity to a given physiologic or pathologic stimulus has virtually been ignored. How is a given force conducted across the intricate extracellular matrix? What is the relative importance of signal recognition systems such as connective tissue RGD ligand interaction with cell membrane integrins or hyaluronic acid with the membrane CD44 proteoglycan
Drug metabolism polymorphisms may be divided into two distinct areas: genetic polymorphisms as determined by direct genotyping of extracted DNA and metabolic polymorphisms as determined by phenotyping with probe compounds. Which of these two methods is most appropriate for clinical investigations is still under debate by geneticists, and the humble rheumatologist may be forgiven for any misuse of pharmacogenetic terminology [1]. Early definitions of a biological ‘polymorphism’ coined by population geneticists were based on phenotypic observations since genotypic studies (by breeding experiments) were difficult to perform. With the advent of molecular biology, the direct measurement of genotype has become possible and geneticists have adopted the genotype as reference. However, it remains that it is the phenotypic expression of the genotype that determines the clinical consequences of a polymorphism [2]. Essentially the two methods should complement one another and hence, associations between phenotypically-determined pharmacogenetic polymorphisms and disease become difficult to interpret without the back-up evidence of genotyping. Until recently, studies of pharmacogenetic polymorphisms in rheumatology, have centred on phenotypic studies comparing the frequency of a given phenotype in health and disease with the inherent consequence of conflicting results.

There may or may not be an association between drug acetylation polymorphisms and RA [3, 4] and idiopathic SLE [5, 6]. A clearer association exists between acetylator phenotype and adverse drug reactions [7] or drug-induced lupus [8]. More recently, the polymorphic form of the enzyme N-acetyltransferase (p-NAT, NAT-2) has been gene sequenced [9] and will allow a clearer picture of any association (or lack thereof) between acetylation and rheumatic disease.

The problem of defining a genetic polymorphism on phenotypic data alone can be highlighted by the metabolism of S-carboxymethyl-L-cysteine (SCMC). This compound has been used as a pharmacogenetic probe of sulphoxidation status [10]. A number of reports have appeared in the literature showing an association between poor sulphoxidation of this mucolytic agent and development of RA and toxicity to D-penicillamine and sodium aurothiomalate [11–14]. The danger here is that contrary to a previous investigation [10], sulphoxidation of this compound has not been proven to be genetically determined and the weight of current opinion supports a non-genetic control over the metabolism of SCMC [15, 16]. The metabolite previously thought to be a sulphoxide of the probe compound has now been shown to be S-carboxymethylthio-L-cysteine, a mixed disulphide [17, 18]. It appears that patients with RA may exhibit a defect in sulphur...