Following the emergence of epigenetics in the research of human disease, great expectations were put in characterizing altered epigenetic pathways as potential targets for therapies. Epigenetic mechanisms are sophisticated networks regulating the expression of genes associated to cell differentiation or to developmental stages. They involve post-translational modifications of histones and genomic cytosines resulting in changes in chromatin conformation.1 Most epigenetic modifications need the active participation of enzymes and cell energetic pathways, and are sensitive to external cues.2 In this way, changes to chromatin conformation can result from exposure to environmental aggressors and account for phenotypic variations of genetic traits. Interestingly, this interaction with environmental factors can be imprinted in cells and individuals, in this way exerting a role on their susceptibility to disease.3

Different studies have shown evidence of a shared aberrant epigenetic signature identifying early phases of tumorigenesis, while an altered expression of epigenetic enzymes, such as histone methyl transferases (HMT) and demethylases (HDM), is commonly observed in cancer cells.4 As a result of this insight, a variety of compounds are currently undergoing development and some of them have already been licensed for the treatment of some tumors. Two types of epigenetic mechanisms have been up to now translated to therapeutics, namely inhibitors of DNA methyltransferases (DNMT) and those of histone deacetylases (HDAC). Both strategies render the re-expression of abnormally silenced lineage specific genes and tumor suppressors, in this way facilitating cell differentiation and growth control.5

A similar approach was enthusiastically conducted in different rheumatic disorders. In the last few years, a vast number of altered epigenetic marks has been described in target cells from patients with these conditions, paving the way for the design of novel therapies.6 A starting hurdle has been to read into some of the contradictory data drawn in different experiments, but on the whole, we are now in a fair position to elaborate theoretical epigenetic models of disease, at least as concerns rheumatoid arthritis and lupus.

As a general overview, rheumatoid synovitis appears to be associated to the silencing of pro-apoptotic molecules, through genomic hypermethylation at differentially methylated regions (DMR) close to their promoters.7 This cancer-resembling signature provides a therapeutic target for the use of DNMT inhibitors. The finding is not surprising, taking that one of the beneficial effects exerted by methotrexate is precisely related to its ability to preclude DNMT1 constitutive activity through the deprivation of S-adenosyl methionine (SAM), which acts as universal donor for methylation reactions.8 An additional interesting target to explore in the disease is the family of histone acetylases (HAT). A local high HAT to HDAC ratio has been consistently found in the microenvironment of rheumatoid synovial tissues as well as in circulating mononuclear cells from the patients. This atmosphere is associated to an open frame conformation of chromatin at nuclear factor kappa B (NFkB) responsive genes, allowing an excessive output of chemokines, adhesion molecules, and some of the pathogenic cytokines of the disease. Interestingly, this unbalanced HAT/HDAC ratio has also been found in the gut of patients with bowel inflammatory disease, and could therefore be taken as a hallmark of dysfunctional inflammation.

As regards epigenetic alterations in lupus, several experimental approaches coincide in demonstrating a combined effect of classical disease triggers, such as UV radiation, hydralazine and procainamide, on lymphocytes.9 On one hand, these agents can block DNMT enzymes, and on the other, they are able to cause DNA damage. Through the former action, target cells increase the expression of immune-reactive factors, and subsequently exhibit a low positive selection threshold. In this sense, T cells from the patients show an abnormally low DNA methylation, particularly during flares, associated to an enhanced expression of costimulatory molecules and interferon responsive elements. In addition, DNMT need to be recruited to regions of DNA damage, where they participate in the DNA repair response (DRR). Therefore, DRR might be compromised in the patients, and this could result in the abnormal persistence of altered chromatin. In turn, chromatin alterations increase its antigenicity. This simple epigenetic model for lupus is quite attractive, since it puts together triggers, cell damage, positive selection and development of anti DNA antibodies which characterize the disease. It also suggests restoration of DNMT enzymes as the principal goal in a hypothetical epigenetic approach of lupus.

But for the use of epigenetic therapies in rheumatic diseases additional hurdles need to be overcome, the first of them being the accessibility of the epigenetic marks needing to be targeted. Although abnormal marks are easier to remove than the
constitutive ones, most epigenetic modifications take place during cell division or in stages of high transcriptional activity. In particular, the use of DNMT modifiers could miss low-proliferating cells, unless used at high doses, at which the hazard of off-target demethylation would be high. However, this approach remains a promising option as part of combined therapies. 10 On the other hand, the huge number of molecules involved in histone modifications, and their relative specificity for a substrate site, has led to an expansion of the search of inhibitors. Again, a major drawback for targeting histone modifiers is that they bear a high noise-to-signal ratio, not only due to a lack of enzyme specificity, but also because histone modifiers play additional roles in the cell machinery, including the DDR, cell cycle arrest, or activation of cytoplasmic metabolic systems. This issue is of little concern when approaching the treatment of advanced cancer, but more difficult to cope with in inflammatory diseases.

Interestingly, between compounds under scrutiny for therapeutic use, some nutrient components have been identified as powerful epigenetic modifiers, and this finding has opened a whole new perspective in the prevention and treatment of cancer. 11 Not in vain, a balanced food intake, physical activity and avoidance of obesity is thought to account for a 30% to 40% prevention of cancer cases. Essential nutrients, such as Fe 2+, Zn 2+ and Mg 2+ , B group vitamins, acetyl coenzyme A, ketoglutarate, NAD+, or S-adenosylmethionine, act as permissive factors for epigenetic modifying enzymes. Accordingly, their deficiency hampers the establishment of physiological epigenetic marks upon cell division. On the other hand, the so-called bioactive food components, typically present in vegetables and fruits, can help re-express constitutive genes abnormally silenced, or shut down inducible responses through the activation of histone modifiers. 12 The principal nutrients under investigation for their therapeutic properties are methyl donors, Se 2-, fatty acids and phytochemicals, and between the latter, flavonoids, retinoids, isothiocyanates, and allyl groups. Short chain fatty acids behave as HDAC inhibitors, and some are currently approved for their use in T cell lymphoma, such as the hydroxamic acid vorinostat, or the epoxides romidepsin, and panobinostat, currently used in combination with bortezomib and dexamethasone in recurrent multiple myeloma. Flavonoids are a large family of polyphenols from different sources, including tea, grapes, berries, celery, and a long etcetera, which act as potent inhibitors of DNMT and HAT, but also play roles as detoxifiers, antioxidants, and inhibitors of protein kinases. Some of them appear to confer protection to the development of cancer, although the extent of this action has yet to be firmly established. 13

On the other hand, the effects of an excessive intake of bioactive food components can have unpredictable effects in different settings, and their use as natural cure or prevention of illness should be discouraged until more clear scientific evidence is available. This issue is of particular relevance, due to the increasing habit of people to try natural remedies aspiring to improve their well-being. Considering their ingredients, some of the marketed nourishment complements are literally epigenetic cocktails, and this is probably a major reason for being rated as beneficial. Most of these compounds have unrestricted access to their consume, in spite of lacking enough information about interactions and dosing. Moreover, there is a relative tolerance to misleading advertising claiming beneficial effects, because they are globally regarded as safe. However, quoting Paracelsus, “nothing is without poison; only the dose permits something not to be poisonous”. Natural components are not necessarily beneficial or harmful, but can yield diverse effects depending on the host, and they might incide in different ways in the context of inflammation, degenerative processes and cancer risk. 11,13

In summary, the impact of epigenetics on human disease and its potential use in therapeutics is only starting to be unveiled. This field has already shifted our conception of how the environment contributes to both evolutionary and individual adaptation. We have also reasons to believe that healthy habits help us keep our physiological epigenetic marks and even overcome potential alterations imprinted in our cells and thereby fight disease. However, we are still far from being able to use this insight in the prevention and treatment of inflammatory diseases. At this point, having good habits, eating a varied diet, and not trusting promised healing properties of nutrition pills are the best recommendations we can offer our patients when asked for advice on how to deal with their conditions.

References

9. Zhang Y, Zhao M, Sawalha AH, Richardson B, Lu Q. Impaired DNA methyla-