# Editorial

# Possible contribution of chronic inflammation in the induction of cancer in rheumatic diseases

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**ABSTRACT**

*Several chronic inflammatory conditions and autoimmune diseases involving different organs and tissues have been found at risk of progression to cancer. A wide array of proinflammatory cytokines, prostaglandins, nitric oxide products, and matricellular proteins are closely involved in premalignant and malignant transition of cells almost always in a background of chronic inflammation.*

*Interestingly, epigenetic perturbations (i.e. miRNA aberrations, altered DNA methylation) together with important steroid hormone metabolic changes (i.e. oestrogens), or the altered vitamin D concentrations that may unbalance the immune / inflammatory response, have been found linked to the risk and severity in several chronic inflammatory conditions, as well as in cancer. In particular, it is evident, that not only the parent oestrogen but also oestrogen metabolites should be taken into account when this process is evaluated, specially the formation of catecholoestrogen metabolites, that are capable of forming either stable or depurinating DNA adducts, which can cause extensive DNA damage.*

*It is interesting that today the successful treatment of several chronic immune/ inflammatory rheumatic diseases is obtained also by using medications initially developed for their use in oncology.*

*The circadian increase of growth factors, specially during the late night, in both chronic inflammation and in cancer patients, as well as the presence of oestrogen-regulated circadian mechanisms, suggests further important links.*

## Introduction

The possible role of inflammation in the development of cancer was described as early as 1863, by Rudolf Virchow, however, the complex role of chronic inflammation in carcinogenesis has been extensively investigated and documented only over the last decades (1). Generally, acute inflammation is a beneficial response that arises to restore tissue injury and pathogenic agents. However, when the acute inflammatory process is unregulated and becomes chronic, concomitant factors might induce malignant cell transformation in the surrounding tissue (Fig. 1) (2).

As matter of fact, several chronic inflammatory conditions and autoimmune diseases involving different organs and tissues have been found at risk of progression to cancer (Table I) (3-23).

Among the mechanisms involved, already recognised are the cell proliferation that is also induced by peripheral oestrogen metabolites, the shifting cellular redox balance toward oxidative stress and, moreover, the increased angiogenesis and increased endothelin 1 (ET-1), that acts in synergism with various growth factors, such as tranforming growth factor beta (TGFbeta), epidermal growth factor (EGF), platalet-derived growth factor (PDGF), fibroblast growth factor (FGF), insulin, to potentiate cellular transformation or replication (24, 25). Microenvironmental contributions, including inflammation, are also driving signals that set off a delicate intracellular feedback loop, such as the endotheliat/epithelial to mesemchymal cell transition (EMT) (Fig. 2) (26).

Altered transcription of genes encoding inflammatory mediators, growth factors, metastatic proteins and angiogenic factors, is the key molecular event in linking inflammation and cancer, together with induction of genomic instability, increased DNA damage and deregulation of cellular epigenetic control of gene expression (27).

Interestingly, a wide array of proinflammatory cytokines, prostaglandins, nitric oxide products, and matricellular

proteins are closely involved in premalignant and malignant transition of cells always in a background of chronic inflammation (28).

The most important biochemical processes that are altered during chronic inflammation and have been implicated in cancer progression are synthesised in Figure 2, including the transition from activated macrophages (M1) into polarised macrophages (M2) and, finally, tumour-associated macrophages (TAMs) (29).

In addition, aberrant intracell signalling pathways comprising various kinases and their downstream transcription factors have been identified as the major contributors in abnormal gene expression associated with chronic inflammation-driven carcinogenesis (30).

Recently, the post-transcriptional regulation of gene expression by microRNAs (miRNA) is also emerging as a crucial condition that provides the molecular basis for linking chronic inflammation to cancer (31).

Important steroid hormone metabolic changes such as the increased peripheral production of oestrogen metabolites and induction of mutations, or the altered vitamin D concentrations that may unbalance the immune/inflammatory response, have been found closely linked to both risk and severity in several chronic autoimmune/inflammatory conditions as well as in cancer (32-38).

Finally, it should be remembered that treatment of chronic immune/inflammatory diseases is obtained by using medications initially developed for use in oncology, such as antiproliferative drugs (*i.e.* methotrexate, cyclophosphamide, azathioprine, etc.), biologic drugs such as B-cell depleting monoclonal antibodies (*i.e.* rituximab), as well as the use of low dose glucocorticoids (39).

We will analyse the integrated effects of some immune-endocrine hormonal modulators (oestrogen metabolite products and vitamin D deficiency) and epigenetic (miRNA aberrations), as important components of the network that links the pathways of chronic inflammation with the possible transition to cancer, in particular in patients with chronic inflammatory and autoimmune rheumatic diseases.

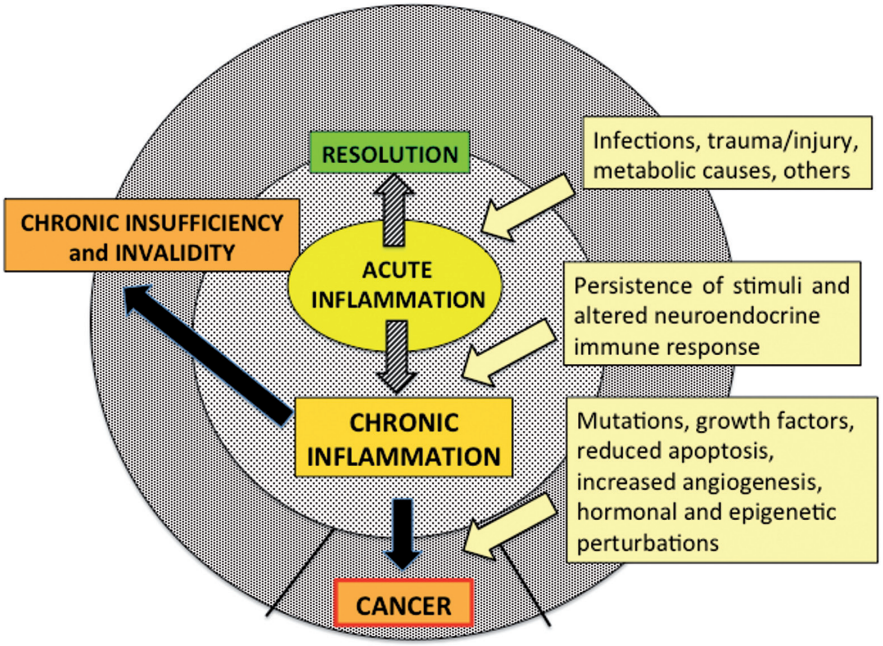


**Fig. 1.** From chronic inflammation to cancer.
Acute inflammation is a beneficial response that arises to restore tissue injury and pathogenic agents, however, when the acute inflammatory process is upregulated and become chronic, the chronic inflammatory reaction induces organ/tissue insuffficiency, or, in presence of concomitant factors (*i.e.* mutations, growth factors, reduced apoptosis, increased angiogenesis, hormonal and epigenetic perturbations) may induce malignant cell transformation in the surrounding tissue (cancer).

## Oestrogen metabolites as risk factors for progression from chronic inflammation to cancer in both sexes

The implications of oestrogens in immunogenicity, cell proliferation, chronic inflammation and cancer risk, represent a complex and progressively integrated pathway that need important consideration (40).

Interestingly, a very recent and large epidemiological study showed that besides the well-known association of risk with sex hormones and insulin-regulated physiological axes, also inflammation-related factors support the development of endometrial cancer (41). As matter of fact, the lifestyle of "Western's people" is characterised by reduced physical activity and excess weight that is, in turn, associated with a number of metabolic and hormonal dysregulations, including increased circulating oestrogen levels, hyperinsulinemia, hyperglycemia, as well as chronic inflammation.

The same altered hormonal and metabolic axes might mediate the association between this lifestyle and the development of endometrial cancer (41).

Interestingly, prediagnostic serum levels of androstenedione, testosterone, dehydroepiandrosterone sulfate, sex hormone-binding globulin, oestrone, oestradiol, together with C-peptide, insulin-like growth factor-binding proteins 1 and 2, adiponectin, glucose and triglycerides, high- and low-density lipoprotein cholesterol have been associated with postmenopausal endometrial cancer risk (41).

Therefore, the relationship between several chronic autoimmune/inflammatory diseases and malignancies has recently been established even when the exact mechanism for carcinogenesis in autoimmunity is not known.

Generally, almost 15–20% of chronic inflammatory conditions (including chronic hepatitis, breast and prostate benign hyperplasia, chronic bronchitis etc), in the presence of other risk factors, might support cancer development (42).

An important role in both oestrogen-driven immune response and cancer, seems to be related to the selection of miRNA, single-stranded non-coding RNAs. In fact, the recently detected selective regulation of miRNA expression in immune cells by oestrogens, is

**Table I.** Cancer associated with chronic inflammatory conditions and chronic immune-mediated rheumatic diseases with cancer associated conditions.

| *Cancer associated with chronic inflammatory conditions* | | |
|---|---|---|
| Patological condition | | References |
| Pancreas cancer | Chronic pancreatitis | 3 |
| Oesophageal adenocarcinoma | Chronic and severe reflux | 4 |
| Colorectal cancer/colitis-associated cancer | Inflammatory bowel disease (ulcerative colitic and Crohn's diseases) | 5 |
| Cholangiocarcinoma | Liver fluke and primary sclerosisng cholangitis | 6 |
| Gastric cancer | Chronic gastritis (H Pylori) | 7 |
| Hepatocellular carcinoma | Infection with heaptitis virus B and C | 8 |
| Gall bladder carcinoma | Gall bladder chronic-sociated cholelytiasis | 9, 10 |
| Endometrial carcinoma | Endometriosis | 11 |
| Prostate cancer | Prostatitis and *E choli* infection of prostate | 12, 13 |
| Lung cancer | Inflammation caused by asbestos, infection, smoking, silica | 14 |
| Melanoma | UV irradiation – associated skin inflammation | 15 |
| *Chronic immune-mediated reheumatic diseases with cancer associated conditions* | | |
| Patological condition | | References |
| Sjögren's syndrome | Lymphoma | 16, 17 |
| Systemic lupus erythematosus | Lymphoma and non-lymphoma malignancies | 18, 19 |
| Rheumatoid arthritis | Lymphoproliferative and solid cancers | 20, 21 |
| Systemic sclerosis | Lung, liver, haematologic, and bladder cancers | 22, 23, 24 |

indicative of an important role of miRNAs in oestrogen-mediated immune diseases in particular in systemic lupus erythematosus (SLE) (43, 44).

On the other hand, miRNAs influence a myriad of biological processes that can contribute to cancer, indeed tumour-suppressive and oncogenic functions have been characterised for some miRNAs (45).

It is evident, that not only the parent oestrogen but also oestrogen metabolites should be taken into account when this process is evaluated (46). In particular, the formation of catecholoestrogen metabolites, which are capable of forming either stable or depurinating DNA adducts, can cause extensive DNA damage and, finally, disease-specific and cancer autoantibodies (Fig. 3) (46-48).

Other important mechanisms involve enzymatic or non-enzymatic oxidation of oestrogen into catecholoestrogen metabolites through semiquinone and quinone redox cycle, to produce free radicals that can cause DNA modifications and contribute to possible progression to cancer (49).

On the other hand, 2-Methoxyoestradiol (2ME2), is an endogenous metabolite of oestradiol that also exhibits disease-modifying activity in animal models of RA and dramatically suppresses development of mouse experimental autoimmune encephalomyelitis (EAE), a rodent model of multiple sclerosis (MS) (50).

Therefore, since 2ME2, has mainly shown antiproliferative (antimitotic) and antiangiogenic properties, interest in it as an anticancer agent is rising (50).

## Sex hormone management in autoimmune rheumatic disorders and cancer

As consequence of their promoting effects on disease progression, the use of oestrogens (oral contraception, oestrogen replacement therapy, treatment of infertility, etc.) must be avoided in patients with active chronic autoimmune disorders in order to reduce the risk of potentiating the immune response and even to induce possible carcinogenesis (51).

On the contrary, androgen-replacement therapy has induced improvements at least in male RA patients and selected SLE patients, whereas, epidemiologic and experimental data have pointed to the key roles of oestrogens in prostate carcinoma development and progression (52-55).

Recently, by studying the functional interplay between the androgen receptor (AR), the orphan nuclear receptor DAX-1 and the aromatase enzyme, a novel mechanism by which androgens, through DAX-1, inhibit aromatase expression in breast cancer cell lines was suggested. This evidence seems to reinforce the theory of androgen-opposing oestrogen action (56).

In fact, aromatase, is frequently highly expressed in the tumour-bearing breast of women diagnosed as having oestrogen receptor (ER) positive tumours, and resulting in dramatically increased local oestrogen production to drive tumour progression (57). On the other hand, it is now evident that prostate is an oestrogen target tissue, and oestrogens directly and indirectly affect the growth and differentiation of the prostate (57).

The precise role of endogenous and exogenous oestrogens indirectly affecting prostate growth and differentiation in the context of benign prostate hyperthrophy (BPH) is complex and might also include local genotoxic effects from oestrogens (58). However, oestrogens and selective oestrogen receptor modulators (SERMs) have been shown respectively to promote or inhibit prostate proliferation, therefore signifying potential roles in BPH (59).

Since serum testosterone levels in men drop by about 35%–40% between the ages of 21 and 85, while oestradiol levels remain constant or increase, this changing androgen: oestrogen (testosterone: oestrogens) ratio under the aromatase effect has been implicated in the

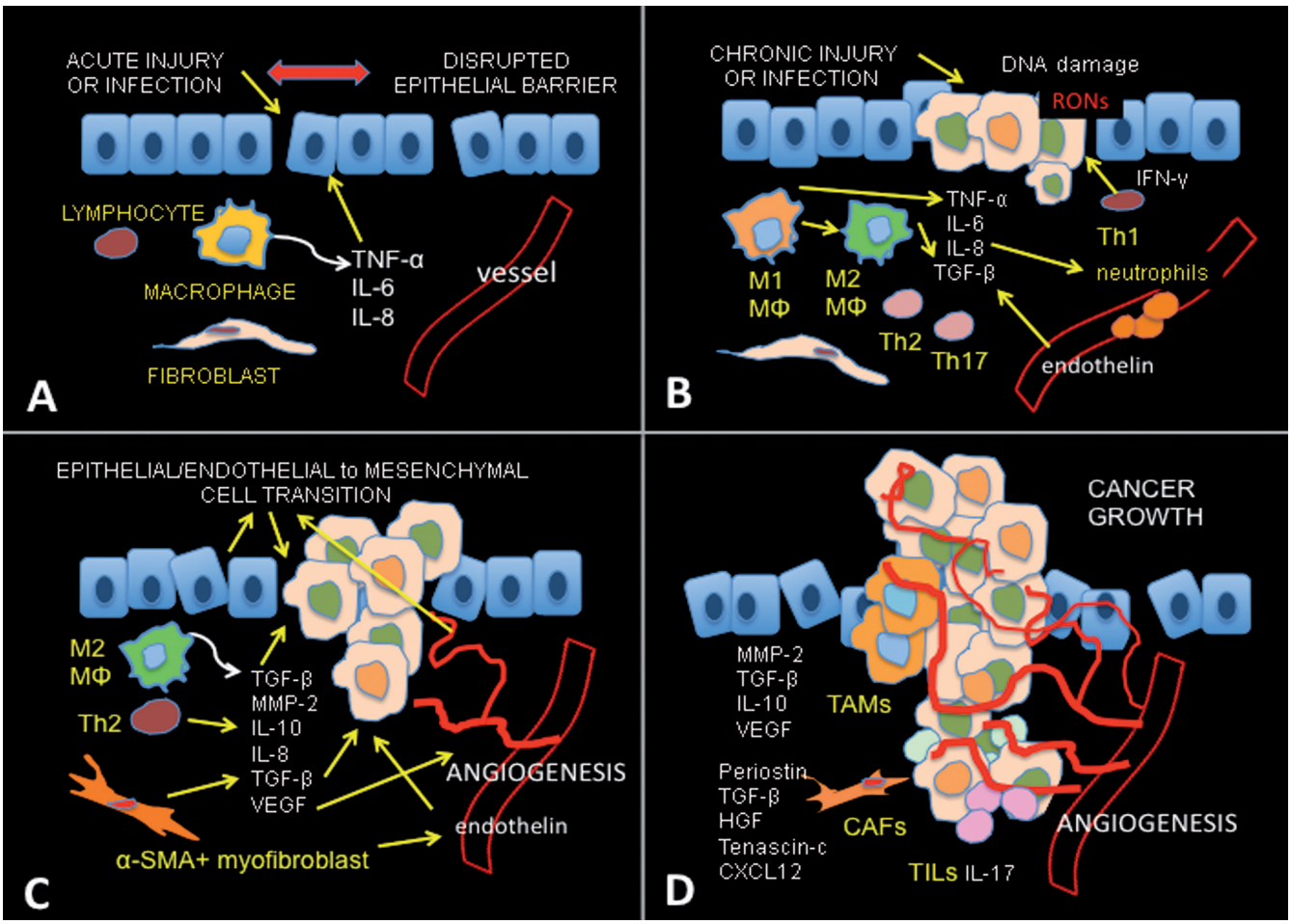


**Fig. 2.** Schematic illustration of the transition from chronic inflammation to cancer (**a-d**).
(**a**) During acute tissue injury or infection, an immune response activates the expression of proinflammatory mediators, such as TNF-α, IL-6, and IL-8 from macrophages and neutrophils.
(**b**) These cytokines can disrupt the epithelial barrier (a), induce reactive oxygen species and nitrogen oxide (RONs) and promote the infiltration of other inflammatory cells. In chronic inflammation, proinflammatory cytokines such as TNF-α, can induce DNA damage through RONS, which may leads to cancer transition initiation.
(**c**) TGF-β together with endothelin-1 (ET-1) can promote malignant transformation through epithelia/endothelial to mesenchymal cell transition (EMT). Cytokines derived from Th1/Th17 lymphocytes, such as IFN-γ IL-10, and IL-17, can participate in further epithelial barrier disruption, as well as the active macropahge (M1) shift into polarised macrophage M2 (phenotypic transitions of macrophages). Cancer growth and invasion are further favoured by proinflammatory cytokines that stimulate cell proliferation, reduce apoptosis, and enhance EMT and angiogenesis; the latter is facilitated by vascular endothelial growth factor (VEGF), CXCL12 (chemokine) and IL-8. Anti-inflammatory cytokines, such as IL-10 (produced mainly by Th2 lymphocytes) and TGF-β contribute to cancer immune evasion.
(**d**) Tumour-associated macrophages (TAM), tumour-infiltrating lymphocytes (TIL), and finally cancer-associated fibroblasts (CAF), together with the myofibroblast phenotype expressing the alpha-smooth muscle actin (aSMA), secrete several factors such as epatocyte growth factor (HGF), periostin, extracellular proteins (*i.e.* tenascin-c) and matrix metalloproteinase 2 (*i.e.* MMP-2) that contribute to cancer growth and metastasis.

development of both BPH and malignant prostate disease (60, 61).

On the other hand, several investigations strongly support an accelerated aromatase-mediated peripheral metabolic conversion of upstream androgen precursors to oestrogen metabolites in peripheral tissues affected by immune/inflammatory reactions, such as synovial tissue in rheumatoid arthritis (RA) in both male and female patients (62, 63). In particular, it was shown that RA synovial cells mainly produce the cell pro-proliferative 16alpha-hydroxyoestrone (16alpha-OHE1) which, in addition to 16alpha-hydroxy-17beta-oestradiol (=oestriol), is the downstream oestrogen metabolite that interferes with proliferation of monocytes (62).

Finally, identification of effective selective SERMs that strongly suppress ERα, as well as specific ligands that promote anti-tumour activities through the ERβ pathway, might contribute to the prevention and treatment of prostatic diseases (usually preceded by chronic gland inflammation) (64). Very recently, the identification of autoantibodies reacting with ER (ERAb) and their possible pathogenic role in autoimmunity and cancer have now opened a new possible pathway and links (65).

On the other hand, treatment of mice with induced SLE, with either the anti-oestradiol antibody or with tamoxifen restored the levels of all the above cytokines to the normal levels as observed in the control mice (66). Finally, murine SLE models with delayed tamoxifen treatment (starting one year after immunisation) also demonstrated beneficial therapeutic effects (67).

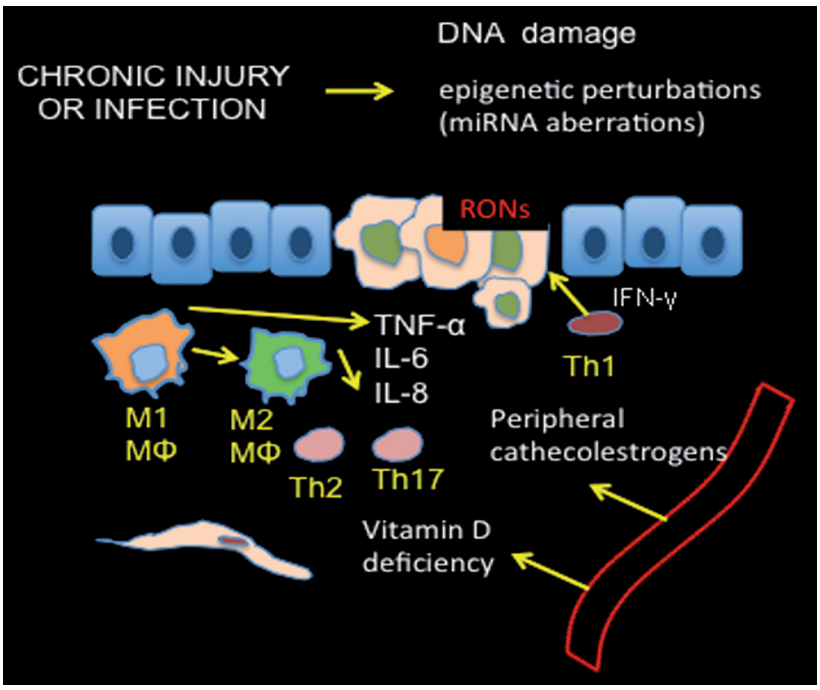


**Fig. 3.** Contribution of immune-endocrine interactions and epigenetic aberrations to the transition from chronic inflammation to cancer.
Oestradiol and oestrogen metabolites, specially the formation of catecholestrogen metabolites, are capable of forming either stable or depurinating DNA adducts, which can cause extensive DNA damage and finally disease-specific and cancer autoantibodies. In addition, calcitriol (1,25(OH)D3) the final metabolite of vitamin D, is considered a true steroid hormone (D hormone), and like glucocorticoids (GCs) and gonadal hormones, may exert several immunomodulatory activities by regulating both innate and adaptive immunity. Finally, genetic and epigenetic perturbations are absolutely required to transform normal cells into cancer cells. To understand the link of so crucial role of miRNAs in chronic inflammation and cancer, an emerging concept must be recognised, namely that DNA damage and repair are linked to cancer (for the terminology see legend to Fig. 2).

**The contribution of vitamin D (D hormone) deficiency to chronic inflammation and cancer progression**

Beyond its critical role in calcium homeostasis, vitamin D has recently been found to play an important role in the modulation of the immune / inflammation reaction by regulating the production of inflammatory cytokines and inhibiting the proliferation of proinflammatory cells, both of which are crucial in particular for the pathogenesis of chronic infilammatory diseases (Fig. 3) (68).

As matter of fact, an association between serum vitamin D concentrations and inflammatory markers in the general adult population has recently been found (69).

Cross-sectional studies have shown that deficient serum levels of vitamin D (25(OH)D) (<20 ng/mL) are present in a significant percentage, not only in patients with chronic autoimmune diseases such as multiple sclerosis (MS), type-1 diabetes, systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), but also in healthy subjects (70).

As matter of fact, calcitriol (1,25(OH) D3) the final metabolite of vitamin D, is considered a true steroid hormone (D hormone), and like glucocorticoids (GCs) and gonadal hormones, may exert several immunomodulatory activities (70).

Interestingly, vitamin D is implicated in prevention and protection from chronic infections (*i.e.* tuberculosis) and autoimmune rheumatic diseases, since it regulates both innate and adaptive immunity, thus potentiating the innate response (monocytes/macrophages with antimicrobial activity and antigen presentation), but suppressing the adaptive immunity (T and B lymphocyte functions) (71).

A prominent endocrine role for 1,25 (OH)D3 in peripheral oestrogen metabolism and related cell proliferative activities has recently been discovered (72). Calcitriol decreases the expression of aromatase, the enzyme that generally catalyses the peripheral oestrogen synthesis from androgens, both in normal and inflammatory conditions, as well as in cancer tissues (*i.e.* breast and prostate cancer), where the oestrogen intracrine synthesis is increased (73).

On the other hand, inflammatory cytokines (IL-6, IL-1, TNF-α) are also strong enhancers of aromatase activity, as reported in chronic inflammatory conditions such as rheumatoid arthritis synovitis (62). Conversely, vitamin D deficiency seems to play a role in increasing autoantibody production by B cells, and seasonal vitamin D declines may trigger flares in RA patients, as-recently shown (74).

Calcitriol seems to exert an inhibitory effect of aromatase transcription by a direct repression *via* promoter II, as well as to exert an indirect effect, due to a reduction in the levels and biological activity of prostaglandins, especially PGE2, which seems to be a major stimulator of aromatase transcription (75).

Recently, an enhanced growth inhibitory effect by combining calcitriol and aromatase inhibitors in breast cancer cell cultures was revealed (75). In addition, it has recently been shown that calcitriol down-regulates the expression of oestrogen receptors and thereby further reduces oestrogen signalling in breast cancer cells, including the cell proliferative stimulus provided by oestrogens (76).

All together, these important new achievements suggest that the inhibition of oestrogen synthesis and signalling by 1,25(OH)D3 and its anti-inflammatory actions might play an important role in the use of calcitriol at least for the potential prevention and/or treatment of breast cancer (77).

From a clinical perspective, the negative consequences of low serum 25(OH) D levels seem to support the protective role of vitamin D in cancer (78). A pooled analysis of two studies with 880 cases and 880 controls demonstrated that individuals with serum 25(OH)D3 of approximately 52 ng/ml had a 50% lower risk of breast cancer than those with levels of 13 ng/ml (79). In addition, a large case-control study on 1394 postmenopausal breast cancer patients

and 1365 controls confirmed that the 25(OH)D serum level was significantly associated with lower breast cancer risk, particularly at levels above 20 ng/ml (80).

Furthermore, one population-based randomised controlled trial found that calcium plus vitamin D supplementation decreased cancer incidence as a secondary outcome, and the dose of 1100 IU/day increased serum 25(OH)D from 29 to 38 ng/ml (81). Interestingly, after 4 years of treatment, the supplemented group showed a 60% lower risk of developing cancer than the placebo group (81). However, in a further randomised trial, the Women's Health Initiative, no effect of calcium and 400 IU vitamin D/day was found on the incidence of breast cancer, probably because the dose was inadequate to efficiently raise the 25(OH)D blood levels (82).

The inflammatory cytokines IL-6 and TNF-α play a critical role both in inflammatory bowel disease, as well as in colorectal tumorigenesis (83). Recently, a colon cancer cell line (COGA-1) was treated with 1,25-dihydroxyvitamin D3 (1,25-D3) or IL-6 or TNF-α, or with their combinations (83). Therefore, the mRNA expression of genes activating (enzyme: 1α-hydroxylase (CYP27B1) or catabolising (enzyme:24-hydroxylase (CYP24A1) vitamin D (1,25-D3) were analysed. As expected, treatment with 1,25-D3 resulted in an upregulation of CYP24A1, whereas expression of CYP27B1 was not affected. On the other hand, treatment with TNF-α and IL-6 led to decreased expression of the vitamin D activating enzyme CYP27B1 (83). These results further support the idea that the presence of proinflammatory cytokines might impair activation of 1,25-D3, limiting its anti-inflammatory action.

Vitamin D also seems to be implicated in susceptibility to inflammatory bowel disease, a predisposing factor in colorectal cancer (84, 85).

## MicroRNA circuits regulate the inflammation-cancer link

Genetic and epigenetic perturbations are absolutely necessary to transform normal cells into cancer cells (86).

MiRNAs, as mediators of the epigenetic effects, are small non-coding RNAs that typically inhibit the translation and stability of messenger RNAs (mRNAs), controlling genes involved in cellular processes such as chronic inflammation, cell cycle regulation, stress response, differentiation, apoptosis, and cell migration (87). They have recently been recognised as powerful regulators of numerous genes and pathways in the pathogenesis of chronic inflammatory and autoimmune diseases (88).

Similarly, miRNAs have been implicated in the regulation of virtually all signalling circuits within a cell and their dysregulation has been shown to play an essential role in the development and progression of cancer (86).

Among miRNAs, miR-181b has been found to be a critical regulatory miRNA linking chronic inflammation and cancer (89). The functional significance of miR-181b in various tumours and translational research suggests that it shows great potential as a predictive and prognostic biomarker (89). On the other hand, candidate miRNA surveys identified increased or reduced expression of selected miRNAs in chronic inflammatory and immune-mediated conditions such as RA (90).

These miRNA seems to exert either pro- or anti-inflammatory effects in multiple cell types or affect osteoclast physiology and the pathogenesis of bone erosion (90).

Recently, increased expression of miRNA-323-3p (miR-323-3p) has been demonstrated in RA synovial fibroblasts (91). The gene encoding miR-323-3p, which is a biomarker in immune and inflammatory responses, occurs in an miRNA cluster in chromosomal region 14q32.31 and might be a new potential marker for RA (91).

Interestlingly, several independent miRNA profiling studies have reported significant differences between SLE patients and healthy controls (87, 92).

Therefore, an increasing number of studies have revealed that miRNAs contributes to the pathogenesis of several autoimmune diseases as recently described for Sjögren's syndrome and systemic sclerosis (SSc) (Fig. 3) (93). In particular, in SSc skin tissues display a different miRNA expression signature than that found in normal controls, showing disregulated miRNAs with pro- or antifibrotic properties and serum miRNA levels are associated with SSc activity and severity (94).

Very recently, besides on miRNAs in SSc, it is emerging that other modifications including DNA methylation have a key role and are also associated with cancer progression (95).

Among other chronic inflammatory diseases, altered miRNAs expression has been recently found also in inflamed and non-inflamed terminal ileal mucosa of adult patients with active Crohn's disease or in patients with chronic obstructive pulmonary disease (COPD) and lung cancer (96, 97).

Furthermore, integrating analysis revealed miRNA-mediated pathway crosstalk among Crohn's disease, ulcerative colitis and colorectal cancer (98).

To understand the link of such a crucial role of miRNAs in chronic inflammation and cancer, an emerging concept must be recognised, namely that DNA damage and repair are linked to cancer. DNA damage that is induced endogenously or from exogenous sources has the potential to result in mutations and genomic instability if not properly repaired, eventually leading to cancer. For example, reactive oxygen species and nitrogen oxide (RONs) produced by inflammatory cells at sites of inflammatory reaction, can induce DNA damage (98). RONs can also amplify inflammatory responses, leading to increased DNA damage (Fig. 3) (99).

This concept is fundamental, and is confirmed by the impressive number of altered miRNAs discovered every day in chronic inflammatory diseases (100). Therefore, the roles of miRNAs in regulating inflammation and DNA repair seem fundamental and, importantly, inflammation and DNA repair are linked in many important ways and, in some cases, balance each other to maintain homeostasis (101).

For example, cancer development seems largerly avoided or delayed in centenarians, where changes in some miRNAs (improving DNA repair) are found in plasma and leukocytes (102). Therefore, miRNAs have been identified that can be considered as senescence-associated

(SA-miRs), inflammation-associated (inflamma-miRs) and cancer-associated (onco-miRs) (102).

The target is now to identify miRNAs alterations that are evident both in chronic inflammation and cancer-associated progression and that might help as biomarkers for the early detection of the transition risk (103).

## Conclusion

Epigenetic perturbations together with important steroid hormone metabolic changes, have been found closely linked to the risk and severity in several chronic inflammatory rheumatic diseases conditions, as well as in cancer.

Interestingly, the positive results obtained in treatment of chronic immune/inflammatory rheumatic diseases by using medications initially developed for their use in oncology, further suggest the presence of linked mechanisms (39).

The concomitant circadian increase of growth factors during the late night in chronic inflammation and in cancer patients, as well as the presence of some oestrogen-regulated circadian mechanisms involved in cell proliferation, should be further investigated (103-107, 111).

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