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Cytokines modulate routes of collagen breakdown

Review with special emphasis on mechanisms of collagen degradation in the periodontium and the burst hypothesis of periodontal disease progression

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Abstract. In this paper, we review recent work on collagen degradation. 2 main routes of breakdown are described and their relevance during healthy and inflammatory conditions of the periodontium is discussed. Special attention is paid to the possible rôle of cytokines, in particular interleukin 1 (IL-1) and transforming growth factor β (TGF- β), on the modulation of collagen phagocytosis and metalloproteinase production. IL-1 has been shown to have a dual function in collagen digestion. It inhibits the intracellular phagocytic pathway, but at the same time, it strongly promotes extracellular digestion by inducing the release of collagenolytic enzymes like collagenase. TGF- β has an opposite effect on both pathways and antagonizes IL-1. Collagenase is released in an inactive form, and a considerable fraction of the proenzyme may become incorporated in the extracellular matrix. This reservoir of latent enzyme can be activated (for instance by plasmin), leading to a sudden and extensive breakdown of the collagenous fibre meshwork. It is suggested that this phenomenon may also take place during progressive periodontitis and could explain an episodic nature of collagenolysis, clinically resulting in bursts of attachment loss (burst hypothesis).

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An important feature of connective tissues in general and the periodontal ligament in particular, is the process of constant renewal of the extracellular matrix components (Everts & Beertsen 1988, Sodek & Overall 1988). Of all connective tissues studied so far it appears that the periodontal ligament has the fastest turnover of collagenous proteins. In rodents the half-life of collagens in the ligament is in order of 1–5 days, which is considerably faster than that in skin (Sodek 1977). This rapid renewal is considered to be important to allow positional adaptation of teeth during function (Sodek, 1989). It is intriguing how the periodontal

ligament is able to provide firm attachment, while at the same time allowing the tooth to undergo processes like eruption and spatial adjustments in the dental arch. Obviously, the metabolism of collagens in the periodontal ligament has to be an accurately controlled balance between synthesis and degradation (Beertsen & Everts 1977, Beertsen et al. 1978).

The breakdown of collagenous proteins occurs via two different pathways: an intracellular and an extracellular route (Fig. 1: Everts et al. (1989), Everts & Beertsen (1992), Murphy & Reynolds (1993), Birkedal-Hansen (1993a), Birkedal-Hansen et al. (1993)).

The Intracellular Route

Under non-pathological conditions phagocytosis and intracellular digestion of collagen fibrils (Fig. 2) is a process observed at a high level in dynamic soft connective tissues such as gingiva and periodontal ligament (Ten Cate & Freeman 1974, Beertsen & Everts 1977, Beertsen et al. 1978, Melcher & Chan 1981, reviewed by Everts et al., (1996)). Although phagocytosed collagen fibrils have been found in osteoblasts, osteoclasts, macrophages, and epithelial cells, fibroblasts appear to be the cell type predominantly involved in this process (Beertsen & Everts 1977,

Fig. 1. The two major routes of collagen breakdown in soft connective tissue: the intracellular and extracellular pathways. (A) The intracellular pathway primarily occurring during normal turnover and remodeling. (A1) Cytoplasmic protrusions surround a collagen fibril, thereby segregating it from the rest of the extracellular matrix and forming a phagosome. (A2) Subsequently, after fusion of a lysosomal vacuole with the phagosome, the proteolytic lysosomal enzymes, such as cysteine proteinases, degrade the fibril intracellularly. (B) The extracellular pathway occurring during excessive breakdown of collagen, e.g. during inflammation or uterus involution. (B1) Following production, procollagenase is released in the extracellular environment where it may be activated (e.g., by plasmin). (B2) Activated collagenase degrades collagenous proteins (in combination with other proteinases such as gelatinase) or it may be inhibited by a tissue inhibitor of metalloproteinases (TIMP). Both pathways are likely to be modulated by cytokines like IL-1 α and TGF- β .

Shore & Berkovitz 1979, Yamasaki et al. 1981, Everts & Beertsen 1988). Intracellular digestion is effected by cysteine proteinases (Everts et al. 1985, 1989), enzymes with a pH optimum in the acidic environment of the (phago)lysosomes. Data from biochemical and morphometric studies have been used to estimate the rate of intracellular collagen digestion and it was concluded that this pathway may be responsible for all collagen breakdown during normal turnover and therefore could be considered as the primary route of collagen degradation in soft connective tissues under steady state conditions (Shore & Berkovitz 1979, Everts & Beertsen 1988, Sodek at Overall 1988,

Fig. 2. Phagocytosis of collagen fibrils by fibroblasts in periosteal explants. (a) Electron micrograph of cytoplasmic protrusion of a fibroblast surrounding a collagen fibril (arrow), thereby segregating it from the rest of the extracellular matrix. 48,750 $\times$ (b) Cross-banded fibrillar collagen (arrows) in phagolysosomes of a periosteal fibroblast. 31,250 $\times$. N: nucleus; G: Golgi apparatus; E: extracellular matrix.

Éverts et al. 1989). In spite of its putative physiological importance (Everts & Beertsen 1992), little is known about the mechanisms involved in the regulation of the phagocytic pathway. Recently, however, evidence was obtained that cytokines may modulate the intracellular pathway of collagen breakdown (Van der Zee et al. 1995a). While TGF- β enhanced collagen phagocytosis, IL-1 α inhibited the process. In combination these cytokines proved to antagonize each other (Table 1).

The Extracellular Route

In pathological situations, such as during periodontal disease, the delicate balance between synthesis and degradation is disturbed. Microbial products may trigger a host response which induces the production and release of cytokines and proteolytic enzymes by both inflammatory and resident cells (Page 1991, Genco 1992, Birkedal-Hansen 1993b). During early gingivitis many of the collagen fibrils in the gingiva are broken down, and replaced by an infiltrate of inflammatory cells, changing a firm, pink gingiva into a swollen, loose and reddish tissue which has lost its integrity (Page & Schroeder 1976). When this condition becomes chronic, pro-

gression of the lesion into periodontitis may eventually occur. During the latter process collagen fibrils of the periodontal ligament that are attached to the cementum are broken down, usually together with the supporting alveolar bone. Subsequent epithelialization of the lesion results in periodontal pocket formation (Page & Schroeder 1976).

Under such pathological conditions a different pathway of collagen degradation is likely to occur: a metalloproteinase-mediated extracellular digestion (Sodek & Overall 1992, Birkedal-Hansen 1993a). Matrix metalloproteinase-1 (MMP-1), or interstitial collagenase, is the best known representative of this group of enzymes. It has the unique capacity to cleave the interstitial collagens types I and III at a single locus of the triple helical body of the collagen molecule which is relatively resistant to other proteinases (Harris & Cartwright 1977) thus producing characteristic N-terminal 3/4 and C-terminal 1/4 fragments.

The action of collagenase is controlled at least at three distinct levels involving production, activation and inhibition (Fig. 3). First, the enzyme is synthesized and secreted in an inactive proform. Second, the enzymes are activated for instance by autoactivation, by

Table 1. Effect of cytokines on collagenase release and collagen phagocytosis by rabbit periosteal explants (derived from Van der Zee et al., (1994, 1995a)).

	EGF	IL-1 α	TGF- β	IL-1 α + EGF	IL-1 α + TGF- β
collagenase release	no effect	stimulation	inhibition	synergistic increase	antagonism
phagocytosis	no effect	inhibition	stimulation	(strong) inhibition	antagonism

Fig. 3. Possible mechanism resulting in a burst of periodontal breakdown. Under the influence of cytokines (e.g., IL-1) a high level of procollagenase is produced and stored in the extracellular matrix (ECM) of the periodontal soft connective tissues. Activation of this enzyme reservoir (e.g., by plasmin) results in a high level of active enzyme that causes a rapid breakdown of collagen fibres, clinically resulting in a burst of loss of attachment. Tissue inhibitors of metalloproteinases (TIMPs) that may also be induced by cytokines (e.g., TGF- β) inhibit the collagenolytic activity and stop further progression of the disease until a newly build-up enzymatic reservoir becomes activated and a new burst occurs.

stromelysin (MMP-3) (Murphy et al. 1987), or by plasmin (Werb et al. 1977, Mignatti et al. 1986). Third, once activated, the enzyme performs its catalytic activity and is subsequently inhibited by specific inhibitors of metalloproteinases (TIMPs) (Welgus et al. 1985a, 1985b, Gavrilovic et al. 1985, Mignatti et al. 1986, Murphy 1991). The production of collagenase, activators and inhibitors is mediated by a variety of compounds among which cytokines like EGF, FGF, PDGF, TGF- β , TNF α , and IL-1 (see Table 2 for abbreviations: (Chua 1985, Murphy et al. 1985, Edwards et al. 1987, Overall et al. 1989, Rifkin et al. 1990, Richards et al. 1991, Meikle et al. 1991, Flaumenhaft 1992)). Therefore, the modulation by cytokines of the cascade of proenzyme-activator-enzyme-

inhibitor (Fig. 3), representing a major pathway of extracellular collagen degradation (Thomson et al. 1989, Werb 1989, Mignatti & Rifkin 1993), is likely to have a high relevance in processes like wound healing (Chowcat et al. 1988, Saarialho-Kere et al. 1992), chronic inflammatory diseases like periodontitis (Heath et al. 1987, Meikle et al. 1989), rheumatoid arthritis (Cambray et al. 1981, McGuire et al. 1981, McCachren et al. 1990, Murphy 1991), and tumor invasion (Moscattelli et al. 1980, Mullins & Rohrich 1983, Mignatti et al. 1986, 1989, Mignatti & Rifkin 1993).

Is there a Relationship between the Intra- and Extracellular Pathways of Collagen Degradation?

Although the relationship between the intracellular and extracellular pathways of collagen breakdown is presently unknown, it is generally taken that, prior to phagocytosis, partial extracellular proteolysis has to occur by collagenase or other MMPs (Harris & Krane 1974, Murphy & Reynolds 1985, Laurent 1987). One may wonder, however, whether collagenase is indeed involved in this process. In this respect it is interesting to note that it has not been possible to demonstrate the presence of collagenase in healthy periodontal ligament, being a tissue with one of the highest physiological collagen degradation rates (Overall et al. 1987). Neither was it possible to influence the level of collagen phagocytosis by blocking collagenase activity with anti-collagenase antibodies or TIMP in cultured periosteal tissue (Everts et al. 1989).

Recently, even a negative correlation was found under the influence of cytokines between the production of procollagenase (collagenase-mediated extracellular pathway) and the level of collagen phagocytosis (intracellular pathway) in rabbit periosteal ex vivo (Table 1). This may be a first indication of a relationship between the two collagenolytic pathways and it may emphasize a role of cytokines in balancing the relative contribution of each route (see also Everts et al. (1996)).

Collagenase and Periodontal Disease

Collagenase that is found in case of periodontitis is derived from the host and not from perio-pathogenic bacteria

(Kryshtalskyj & Sodek 1987). The presence of two distinct types of collagenases has been described: the 57/52 kD (MMP-1) and the 75 kD form (MMP-8). The former enzyme is produced and released as an inactive proenzyme by many periodontal cell types including fibroblasts but also macrophages, endothelial cells, epithelial cells, Langerhans cells, and osteoblasts (Birkedal-Hansen 1993a). This form is also known as interstitial collagenase or 'fibroblast-type' collagenase. MMP-8 is derived from neutrophils where it is stored intracellularly in granules ('neutrophil-collagenase') (Sorsa et al. 1992).

Although there is no direct evidence for a causal relationship between metalloproteinases and periodontal tissue destruction, the involvement of collagenase in collagen degradation during chronic inflammatory periodontal disease is highly suggestive and based on a vast amount of studies. MMP-8 is detected at high levels in gingival crevicular fluid and saliva during gingivitis or periodontitis whereas it is undetectable in healthy individuals (Sorsa et al. 1992, Ingman et al. 1993). Moreover, a positive correlation has been shown between the amount of this enzyme and the level of disease activity (Kryshtalskyj et al. 1986) and a negative correlation between the enzyme level and the intensity of periodontal treatment (Golub et al. 1976, Kowashi et al., 1979 Lamster et al. 1985, Larivée et al. 1986, Vilella et al. 1987, Hakkaraian et al. 1988). Furthermore, in extracts or homogenates of diseased periodontal tissues MMP-1 is abundantly present in contrast to healthy specimens and, as with MMP-8, a positive correlation was found between the presence of the enzyme and the severity of inflammation (Overall et al. 1987, Sorsa et al. 1988, Robinson et al. 1992). In addition, MMP-1 has been immunolocalized in inflamed but not in healthy periodontal tissue (Woolley & Davies 1981). More recently it was shown that mRNA expression for collagenase and TIMP is enhanced in diseased gingiva (Nomura et al. 1993, Tonetti et al. 1993). Following initial periodontal treatment however, Meikle et al. (1994) could not find detectable levels of MMP-1 in fresh gingival biopsies.

The relative contribution of MMP-8 and MMP-1 in the pathogenesis of periodontitis is still not entirely clear and needs further investigation. It has been shown that most if not all collagenase

Table 2. List of abbreviations

EGF:	epidermal growth factor
FGF:	fibroblast growth factor
IL-1:	interleukin 1
MMP:	matrix metalloproteinase
PDGF:	platelet-derived growth factor
TGF:	transforming growth factor
TIMP:	tissue inhibitor of metalloproteinases
TNF:	tumor necrosis factor

in gingival crevicular fluid or saliva of patients with adult periodontitis is derived from neutrophils (MMP-8), without detectable levels of MMP-1 (Sorsa et al. 1988, 1992, Sodek & Overall 1992). On the other hand, immunolocalization of MMP-1 in inflamed periodontal tissues showed a strong labeling and association between the presence of the enzyme and resident connective tissue cells (Woolley & Davies 1981). These data may suggest that, following production during inflammation, most MMP-1 remains in the gingival tissue, whereas the vast majority of released MMP-8 finds its way to the pocket.

Cytokines Mediate Collagenase Production

During the last 2 decades numerous biological effectors have been elucidated which participate in the regulation/modulation of MMP-mediated collagen degradation. As mentioned above, cytokines, being polypeptides which mediate cell metabolic processes, appear to play a crucial role in this process. Also periodontitis is strongly associated with the presence of cytokines, such as IL-1 α and β and indeed many cell types in the periodontium have the capacity to produce these compounds (Mundy 1991, Birkedal-Hansen 1993b). In inflamed gingiva, however, macrophages were found to be the prime IL-1 mRNA expressing cells (Matsuki et al. 1993). Although the rate of IL-1 α and β expression was similar, in gingival crevicular fluid IL-1 α was the predominant active cytokine (Matsuki et al. 1993). A positive correlation was found between the presence and activity of periodontal disease and the level of this cytokine in tissue extracts (Honig et al. 1989, Jandinski et al. 1991, Stashenko et al. 1991, Matsuki et al. 1993) or gingival crevicular fluid (Charon et al. 1982).

The role of cytokines in the pathogenesis of periodontal disease is probably rather complex. There is ample *in vitro* evidence, however, suggesting that these compounds are involved in the regulation of metalloproteinase production and activity which eventually results in loss of periodontal attachment. First, it was shown that fibroblasts of periodontal tissues produce MMP-1 as well as inhibitor molecules *in vitro* (Pettigrew et al. 1980, Heath et al. 1982) their production being mediated by cytokines. In particular IL-1 proved to

be extremely potent in inducing proMMP-1 production by many cell types, including fibroblasts of the gingiva and periodontal ligament (Lark et al. 1990, Richards & Rutherford 1988). On the other hand, TGF- β , a cytokine known for its wound healing and repair-stimulating activities (Roberts & Sporn 1993), has a downregulating effect on MMP-1 expression, synthesis, and release, and moreover appears to neutralize the activity by stimulating the production of TIMP (Overall et al. 1989).

Studies on the effects of combinations of various cytokines are of interest, since they may act in a synergistic or antagonistic fashion (Lynch et al. 1987, Chandrasekhar & Harvey 1988, Andrews et al. 1989, MacNaul et al. 1990, Circolo et al. 1991, Tingström et al. 1992). Recently, it was demonstrated that IL-1 α in combination with EGF synergistically enhances the production of procollagenase by periosteal tissue explants up to 100-fold (Van der Zee et al. 1993). TGF- β , on the other hand, induces an inhibition of procollagenase release (Overall et al. 1989, Van der Zee et al. 1995a). When IL-1 α and TGF- β are added in combination an antagonistic effect is observed (Chandrasekhar & Harvey 1988, Andrews et al. 1989, Van der Zee et al. 1995a, b). Members of the TGF- β superfamily (TGF- β s and bone morphogenetic proteins) appear to be essentially anabolic growth factors promoting deposition of stroma (Roberts et al. 1986, Overall et al. 1989, Roberts & Sporn 1993) whereas cytokines like IL-1 and TNF α are generally proinflammatory mediators inducing transcription of MMP genes which eventually results in resorption (Dayer et al. 1985, McCachren et al. 1989, Saito et al. 1990, Takakis 1993).

Another process mediated by cytokines like IL-1 α , EGF and TGF- β is the resorption of bone (Raisz et al. 1980, Gowen et al. 1983, Gowen & Mundy 1986, Lorenzo et al. 1988, Pfeilschifter et al. 1988, Takakis 1993). Although bone resorption should probably be considered as a distinct degradative pathway with a central rôle played by the osteoclast (Birkedal-Hansen, 1993a), collagenase also appears to be involved at least in some steps of this process like breakdown of the collagen fringe prior to and following osteoclastic bone resorption (Everts et al. 1994) as well as in the actual osteoclast

mediated bone resorption (Delaissé et al. 1993, Hill et al. 1994, 1995). Lorenzo et al. (1988) demonstrated that bone resorption of rat long bone cultures is enhanced by EGF or IL-1 α and that a combination of both cytokines resulted in additional effects. Recently, a comparable effect of cytokines in rabbit calvariae was found together with a concomitant increase in the release of the metalloproteinases, collagenase and gelatinase, and tissue inhibitor of metalloproteinases (TIMP), suggesting that MMP-mediated steps in bone resorption are also modulated by cytokines (Van der Zee et al. in preparation).

Cytokine-induced Reservoir of Latent Collagenase in Extracellular Matrix: a Possible Mechanism for a "Burst" of Periodontal Breakdown

Several studies have suggested that periodontitis has a cyclic behavior being characterized by relatively short periods of exacerbation during which progressive loss of attachment occurs followed by periods of remission (Goodson et al. 1982, Socransky et al. 1984, Goodson 1992, Cohen 1993, Machtei et al. 1993a, 1993b). Understanding of the pathogenesis of periodontitis is important for an optimal treatment and prevention of the disease. Therefore, it is of considerable interest to know when, how and why progression of periodontitis occurs. Periods of progressive loss are likely to involve significant proteolysis during a relatively short time-interval. Such a proteolytic burst can be explained by assuming that a sudden increase occurs in the synthesis and/or release of catabolic enzymes (e.g. MMP-1/MMP-8). Alternatively, a similar excessive proteolytic activity could occur if these proteolytic enzymes are stored at high concentrations in the extracellular matrix and suddenly become activated. In support of this latter mechanism are recent *in vitro* data demonstrating that a vast amount of procollagenase can become incorporated into the extracellular matrix of cultured soft connective tissue (periosteum) without resulting in degradation (Van der Zee et al. 1994). Activation of this matrix-stored enzyme fraction by plasmin (considered to be a putative physiological activator), resulted in a rapid breakdown of the bulk of the collagenous proteins present (70%) (Van der Zee et al. 1996). The activation process may be regarded as a rate-limiting step

in this MMP-1-mediated collagenolysis (Birkedal-Hansen et al. 1992).

These recent findings illustrate that procollagenase, produced over a longer time period, can be stored as a reservoir with a high potential of proteolysis following activation. This in combination with the findings by Woolley & Davies (1981), demonstrating immunohistochemically that collagenase is present at a high level in the extracellular matrix of diseased human gingival tissue, but absent in biopsies of healthy or treated sites, and the findings by Overall et al. (1987), who found that inflamed gingiva indeed contains tissue bound collagenase and that the presence of the enzyme corresponds with the level of inflammation, may in part explain a mechanism contributing to the cyclic nature of disease progression ('burst hypothesis') in case of periodontitis. Activation of tissue-stored procollagenase may cause a sudden period of progressive loss of attachment. During a period of remission a balance is reintroduced for instance by TIMPs (Fig. 3). Subsequently, when the chronic inflammatory reaction takes over again, a reservoir of proenzyme is gradually being stored in the matrix until, following activation, a new burst occurs. As the interactions between cytokines – proenzymes-activators and inhibitors are considered to be very local processes, they could contribute to the site-specific nature of the proteolytic episodes in periodontitis (Goodson et al. 1982, Socransky et al. 1984).

Conclusions

Based on numerous observations published over the last two decades, it is concluded that under physiological steady-state conditions, collagen is broken down primarily via the intracellular pathway. Under pathological conditions (e.g. inflammation) cytokines like IL-1 α are released which on one hand may induce the production and release of collagenolytic enzymes and on the other hand are likely to inhibit the phagocytosis of collagen. Following the release of procollagenase a substantial fraction of the proenzyme is incorporated in the extracellular matrix. During inflammatory conditions such a reservoir of latent enzyme could be activated, leading to a sudden and extensive breakdown of collagen. If this phenomenon indeed takes place in periodontitis, it may at least in part provide

an explanation for the episodic nature of collagenolysis resulting in bursts of attachment loss ('burst hypothesis'). Other cytokines, like TGF- β , may counterbalance these effects during phases of remission or healing, and contribute to restoration of a state of equilibrium.

Zusammenfassung

Zytokine beeinflussen die Wege des Kollagenabbaus. Übersichtsartikel mit besonderer Betonung der Mechanismen des Kollagenabbaus im Parodont und der Ausbruch-Hypothese bei progredienter Parodontalkrankheit

In diesem Referat besprechen wir neuere Arbeiten, die sich mit dem Abbau des Kollagens beschäftigen. Die beiden hauptsächlichen Wege des Kollagenabbaus werden beschrieben, sowie ihre Bedeutsamkeit bei gesundem und durch entzündliche Vorgänge veränderten Parodont. Besondere Aufmerksamkeit wird der in Betracht kommenden Rolle der Zytokine, vor allem des Interleukins 1 (IL-1) und des transformierenden Wachstumsfaktors β (TGF- β), hinsichtlich der Beeinflussung der Kollagenphagozytose und der Metalloproteinasebildung gewidmet. Wie gezeigt werden konnte, hat IL-1 bei der Verdauung des Kollagens zweierlei Funktionen. Es hemmt den interzellulär-phagozytären Verlaufsweg, fördert aber gleichzeitig die extrazelluläre Digestion kräftig und zwar durch Freisetzung kollagenauflösender Enzyme, wie der Kollagenase. TGF- β verhält sich dagegen hinsichtlich der Verlaufswege genau umgekehrt und gegenüber dem IL-1 antagonistisch. Die Kollagenase wird in inaktiver Form freigesetzt und die extrazelluläre Matrix kann eine erhebliche Fraktion des Proenzym aufnehmen. Dieses latente Enzym-Reservoir kann aktiviert werden (z.B. durch Plasmin), mit plötzlich aufkommendem und umfangreichem Abbau des kollagenen Faser-netzes als Folge. Es wird der Eindruck vermittelt, daß dieses Phänomen auch bei progressiver Parodontitis vorkommen kann. Dadurch könnte die episodische Eigenart der Kollagenolyse erklärt werden, die klinisch als das Aufkommen plötzlich aufflammender Attachmentverluste in Erscheinung tritt (Ausbruch-Hypothese).

Résumé

Voies modulées des cytokines de la destruction du collagène. Revue insistant sur les mécanismes de la dégradation du collagène dans le parodont et sur l'hypothèse de flambées de progression dans la maladie parodontale

Sous les conditions physiologiques, en état normal, le collagène est détruit principalement via la voie intracellulaire. Sous des conditions pathologiques (par exemple l'inflammation) des cytokines comme l'interleukine-1 sont libérées et peuvent d'une part induire la production et la libération d'enzymes

collagénolytiques et d'autre part inhiber la phagocytose du collagène. Suite à la libération de procollagenase une importante fraction du proenzyme est incorporée dans la matrice extra-cellulaire. Sous les conditions inflammatoires un tel réservoir d'enzymes latents pourrait être activé, entraînant une destruction rapide et importante du collagène. Si ce phénomène prend place durant la parodontite et il peut en partie du moins apporter une explication à la nature épisodique de la collagénolyse se produisant par flambées de perte d'attache. D'autres cytokines tel le facteur transformant la croissance- β , peuvent contrebalancer ces effets durant les phases de rémission ou de guérison, et contribuent à la restauration d'un état d'équilibre.

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