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IL-1β at the crossroad between rheumatoid arthritis and type 2 diabetes: may we kill two birds with one stone?

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Summary

Although in the past the prevention of joint destruction in rheumatoid arthritis (RA) was strongly emphasized, now a great interest is focused on associated comorbidities in these patients. Multiple data suggest that a large percentage of RA patients are affected by Type 2 Diabetes (T2D), whose incidence has reached epidemic levels in recent years, thus increasing the health care costs. A better knowledge about the pathogenesis of these diseases as well as the mechanisms of action of drugs may allow both policy designers and physicians to choose the most effective treatments, thus lowering the costs. This review will focus on the role of Interleukin (IL)-1β in the pathogenesis of both the diseases, the efficacy of IL-1 blocking molecules in controlling these diseases, and will provide information suggesting that targeting IL-1β, in patients affected by both RA and T2D, may be a promising therapeutic choice.

Keywords: Rheumatoid Arthritis; Type 2 Diabetes; IL-1β; macrophage; pathogenesis, biologic drug, IL-1 blocking agents.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease in which tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) play a key role in the induction and progression of the disease. Therapies, antagonizing their effects, have been shown to be effective in controlling the symptoms as well as the activity of RA [1-3]. Several reports and data from registries confirm that the prevalence of type 2 diabetes mellitus (T2D) is increased in RA patients [4]. Several data, in recent years, showed that the excess of nutrients, secondary to over-nutrition, may activate the immune system [2], leading to an increased production of inflammatory cytokines, and suggested that an inflammatory-mediated process, mainly mediated by IL-1β, may be associated to T2D pathogenesis [1]. The magnitude of metabolic stresses, associated with a genetic predisposition, may lead to a continuous immune activation culminating into the disease [1-3]. These alterations are usually recognized in obese individuals, a condition frequently observed in RA patients, due to both inflammatory process and lifestyle changes, in which hypoxia, deriving from the uncoupled growth of adipose tissue and vasculature, recruits activated macrophages into the tissue, thus providing the pathological link between adipose tissue expansion and inflammation [5,6]. Recently, several data have been reported about metabolic syndrome, insulin resistance, T2D and activation of the immune response, confirming the involvement of IL-1β in the recruitment of activated immune cells into pancreatic islets, in the β-cell apoptosis and islets fibrosis, as well as the efficacy of IL-1 blockers in controlling [7] these deleterious effects

This review focusing the pathogenic role of IL-1β in the pathogenesis of both RA and T2D, the efficacy of IL-1 blocking agents in controlling these different but frequently associated diseases, will provide information suggesting that targeting IL-1β may be, in the future, a promising therapeutic choice in patients affected by both the diseases.

IL-1β production and release

The IL-1 family includes 11 members and among them, IL-1β plays a key role in many inflammatory diseases [8]. IL-1β is produced as inactive precursor, the pro-IL-1β, and after its proteolytic cleavage by active caspase-1, the active form of IL-1β, may be release. Caspase-1 activation requires the oligomerisation of the inflammasome, a complex intracellular proteic platform [9]. The inflammasome platform may prevent a uncontrolled production of IL-1β. In fact, patients with a genetically mediated deregulation of caspase-1 activation, leading to a continuous IL-1β production, develop a severe multi-organ sterile inflammations, such as cryopyrin-associated periodic syndrome and Muckle-Wells Syndrome [8-10].

IL-1β is mainly produced by cells of innate immune system, [11] after its release, binds 2 surface receptors, IL-1 type I (IL-1RI) and IL-1 type II (IL-1RII). These receptors show a single transmembrane domain associated with an IgG-like extracellular domain. IL-1RI ~~shows~~ displays a conserved region of 212 amino acids in the cytoplasmic tail, the Toll/IL-1R domain. IL-1RII contains

a signalling-incompetent intracellular domain of 29 amino acids that negatively regulates IL-1β signalling by serving as a docking site for IL-1β, thus preventing IL-1β/IL-1RI interaction. After IL-1β binding, IL-1RI undergoes a conformational change linking the interleukin 1 receptor accessory protein (IL-1RAcP) to form the IL-1RI/IL-1β/IL-1RAcP hetero-complex, leading to the recruitment of downstream signalling molecules, such as the myeloid differentiation primary response gene 88 (MYD88) and interleukin-1 receptor-activated protein kinase (IRAK) 4, 2 intracellular adaptor proteins, are assembled by conserved cytosolic regions called Toll- and IL-1R-like (TIR) domains. The IRAK4 phosphorylation precedes the phosphorylation of IRAK1, IRAK2 and tumor necrosis factor receptor-associated factor (TRAF) 6. The latter is an ubiquitin E3 ligase, that after association with ubiquitin E2 ligase complex, attaches K63-linked polyubiquitin chains to different IL-1 downstream intermediates, including TGF-β-activated protein kinase (TAK-1). After TRAF6/TAK-1 association, many transcription factors, such as NF-κB, and AP-1, which are involved in the inflammatory response, may be activated [8-12]. Furthermore, exogenous microbial products or exogenous cytokines, such as TNF-α IL-18, or IL-1β itself may provide additional signals, inducing the synthesis of IL-1β mRNA [8-12].

A natural IL-1 Receptor Antagonist (IL-1RA), lacking agonistic activity in humans, is produced to modulate the IL-1β activity. IL-1RA, saturating both the binding sites of IL-1R and blocking the recruitment of IL-1RAcP, inhibits the formation of the IL-1RI/IL-1β/IL-1RAcP hetero-complex thus stopping the downstream cascade [13].

RA and IL-1β pathogenesis

A large number of evidence in experimental models of arthritis as well as in humans confirmed the role of IL-1β in RA pathogenesis [14]. In fact, the synovial fluid of RA patients shows high IL-1β levels, produced by synovial tissue macrophages, activated T cells, fibroblasts and chondrocytes [15]. In affected joints, IL-1β modulates leucocyte recruitment, as well as the induction of matrix metalloproteinases (MMPs) and an higher tissue turnover [15,16], inducing cartilage degradation and inhibition of new matrix synthesis, thus leading to joint destruction, as confirmed in different animal models, in which the overexpression of IL-1β induces joints damage mirroring the pathology of RA [17]. Furthermore, IL-1β stimulates osteoclast differentiation and activity, via receptor activator of a nuclear factor kappa-B ligand (RANKL) expression in both the synovial fibroblasts and T cells of RA patients, a mechanism involved in bone erosion [18-22]. In addition, a vicious amplification loop, including IL-1β, TNF-α and IL-6, may contribute to the bone loss, via the modulation of synovial leucocyte infiltration and pannus organization [13]. Furthermore, in experimental RA models, spontaneous poly-arthropathy and bone erosions may be observed after deletion of the gene encoding for IL-1RA [20-25]. On the contrary, a reduction of the cartilage breakdown associated with a preservation of cartilage matrix synthesis may be observed after the intra-articular transfer of the human IL-1RA gene in experimental models [26,27]. Finally, the

antagonism of IL-1β by using neutralizing antibodies, in adjuvant arthritis model, strongly decreased the disease activity [23,24].

The role of mononuclear cells in the production of IL-1 β during RA

Bone marrow progenitors, circulating monocytes, and tissue macrophages populate lymphoid and non-lymphoid tissues; an imbalance of their function may contribute to the RA pathogenesis as well as the development of comorbidities [28].

Two different subsets of macrophages, called M1 and M2 cells, mirroring what observed for Th1 and Th2 nomenclature, may be identified. M1 macrophages are activated by inflammatory stimuli such as interferon (IFN)-γ, granulocyte macrophage colony-stimulating factor (GM-CSF), IL-1β and TNF-α, and express higher levels of inflammatory cytokines, such as TNF-α, IL-1β, IL-6, IL-23, IL-12, reactive nitrogen intermediates (RNI), reactive oxygen intermediates (ROI), and chemokines, thus displaying a pro-inflammatory activity. On the contrary, activated M2 macrophages are induced by IL-4, IL-13, macrophage colony-stimulating factor (M-CSF), IL-10, and corticosteroids [29], express higher levels of IL-4, IL-10, CD163, CD206, and chemokine (C-C motif) ligand (CCL)16, 17, 18, 22, and 24, thus promoting wound healing and immune modulatory/suppressive activities [30]. During RA, increased levels of both GM-CSF and M-CSF may be observed in the synovial fluid, thus contributing to the joint inflammation via the activation of M1 macrophages. Furthermore, several inflammatory cytokines modulate the overproduction of GM-CSF and M-CSF by synovial fibroblasts and chondrocytes, thus inducing a self-perpetuating vicious loop [31]. In RA patients, the normal balance between these 2 macrophage subsets may be restored by conventional therapies and/or biologic agents [28-30].

It is well known that T cells play a major roles in RA pathogenesis. In fact, RA is considered an autoimmune pathology in which autoreactive T cells are activated and involved in all the pathogenic steps of the disease. T cells, by the interaction with an unidentified antigen, proliferate and activate in early phases of the disease and directly drive the chronic inflammatory process [31]. Available literature confirms that T cells are activated and accumulated in the inflamed synovium, thus leading to perpetuation of the chronic inflammation and tissues remodeling and destruction. On these bases, experimental therapies targeting autoreactive T cells have been developed, including clinical trials with of anti-CD4 monoclonal antibodies, induction of oral tolerance, T cell vaccine and peptide therapy [32]. Although the preliminary results are encouraging, further studies are needed to fully elucidate the efficacy as well as the safety of these immunotherapies.

IL-1 blocking agents for RA

Anakinra, a recombinant form of a human IL-1RA, is a biologic drug antagonizing ~~IL-1 activity~~. both IL-1β or IL-1α activity. This drug showed, in several clinical studies, a significant improvement in

signs and symptoms of RA [33]. A systematic review of literature, confirmed a significant clinical improvement in anakinra treated patients groups, associated with a significant lowering of radiographic progression [33]. In addition, no opportunistic infections and reactivation of latent infection of Mycobacterium tuberculosis was observed, confirming the good safety profile of this drug [33]. Finally, anakinra decreased the daily intake of glucocorticoids in RA patients enrolled in the clinical trials [33], a significant added benefit, considering the deleterious effect of steroids long treatment.

Canakinumab is a fully human anti-interleukin IL-1β monoclonal antibody, approved for the treatment of cryopyrin associated periodic syndrome [34]. Recently, it has been tested for the RA treatment [35,36]. Its efficacy was assessed in a proof-of-concept study enrolling 53 active RA patients treated by methotrexate. The results showed that canakinumab significantly reduced the disease activity in enrolled population [35]. More recently, both the efficacy and safety of canakinumab, in RA patients, were evaluated in a phase II, randomized, double-blind, placebo-controlled trial, enrolling 274 patients. Patients were randomized to receive, in addition to methotrexate, , canakinumab or placebo every 2 weeks. The reported data showed that a large percentage of patients, treated with canakinumab, reached a significant clinical improvement when compared with placebo group without any concern about infection [36].

IL-1β and T2D

Increased levels of glucose and free fatty acids (FFAs), such as oleate, palmitate and stearate may be able to induce an overproduction and release of inflammatory cytokines and chemokines by immune cells, adipose tissue, pancreatic islets and other insulin sensitive tissue. As far as the pancreatic islets are concerned, the final result of this process is the development of β-cell dysfunction and apoptosis, resembling both T1D and T2D pathogenesis [1-3].

Although in both pancreatic islets and adipose tissue the mechanisms of glucose induced activation of IL-1β are not fully understood, several observations have been reported concerning a possible link between immune cells and development of T2D [7].

As far as the ability of increased glucose levels to modulate the production of inflammatory cytokines is concerned, conflicting results may be available in literature. Maedler et al. showed that higher glucose levels were able to up-regulate the secretion and function of molecules involved in the inflammatory process, such as IL-1β, NF-κB and Fas [37]. On the contrary, Welsh et al. failed to confirm these results in the cultures of the human islets stimulated with different concentrations of glucose [38]. At present, further studies need to better elucidate the role of IL-1β in the pathogenesis of T2D.

Glucose-induced IL-β production may involve the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome [1-3]. Specifically, the increased levels of glucose induce the dissociation of thioredoxin-interacting protein (TXNIP) from thioredoxin, under the influence of ROI. Successively, the interaction of TXNIP with the NLRP3-inflammasome, activating caspase 1,

modulates the release of IL-1β [39]. Although in this context, the pathogenic mechanisms of ROI are not still fully clarified, it must be pointed out that the β-cells display a very low reservoir of antioxidative enzymes, being more vulnerable to oxidative stress [1-3].

In the later stages of T2D, the deposition of amyloid in the islets further contribute to the release of IL-1β, via the activation of NLRP3-inflammasome [40]. Interestingly, deposition of amyloid in the islets is a hallmark of T2D, and human islet amyloid polypeptide (IAPP) seems to be related with the induction of IL-1β secretion both in macrophages and β-cells [40]. In addition, several other mechanisms have been proposed to explain the toxic effects of amyloid on β-cells, such as ER stress, defects in autophagy, enhanced production of pro-inflammatory cytokines, mitochondrial membrane damage, permeabilization of cell membranes, activation of Calpain-2, receptor-mediated mechanisms linked to oxidative stress, and finally the activation of cell death signaling pathways [41].

As far as FFAs and their metabolites are concerned, it has been suggested that FFAs may act as either pro- or anti-inflammatory agents depending on the chemical structure. Saturated fatty acids (SFA) and polyunsaturated fatty acids (PUFA) significantly differ in their contributions to inflammation [42]. While SFAs have been shown to induce inflammation, PUFAs display an anti-inflammatory effects by downregulating NF-kB, IL-1β, TNF-α and IL-6. It has been suggested that SFAs may activate G protein-coupled receptors (GPCRs), thus promoting the production and release of inflammatory cytokines such as IL-1β, IL-6 and TNF-α. In addition, SFAs, binding to Toll Like Receptors (TLR), mainly TLR2 and TLR4, peroxisome proliferator-activated receptors (PPARs) and GPCRs may further increase the inflammatory process. [42-45].

In this setting, the inflammasome, in presence of a possible metabolic stressor, may act as a sensor of metabolic danger, thus inducing IL-1β production and leading to the tissues damage [43]. Furthermore, a vicious cycle of auto-inflammation may be observed in purified human β-cells, that after stimulation with IL-1β, increase their production and release of the same cytokine thus perpetuating the inflammation [44]. It has been shown that IL-1β auto-stimulation may be prevented by reducing NF-κB activity or, alternatively, by blocking IL-1R1 signalling, the latter also inhibiting FFAs- and glucose-induced upregulation of IL-1β [45].

In addition, a failure in the anti-inflammatory axis has been shown, in the T2D patients, that display lower levels of IL-RA, in the endocrine pancreas, when compared to healthy controls [2, 46].

Finally, the evidence that hyperglycaemia may directly induce β-cell apoptosis, via the expression of the pro-apoptotic receptor Fas on β-cells, which may be further upregulated by glucose-induced IL-1β production by β-cells, confirms the metabolic trigger for the inflammatory process in T2D islets [1-3,47,48].

Thus, we may suggest that the insulin deficiency, observed in T2D, is linked to different factors, such as lipotoxicity, glucotoxicity and amyloids deposits which are able to induce IL-1β overproduction, leading to β-cell dysfunction and subsequent T2D [40].

The role of monocytes/macrophages and production of IL-1β during T2D

The T2D is associated with the production of higher levels of inflammatory cytokines, which recruit immune cells into pancreatic islets [49]. It must be pointed out that resident macrophages, generally exhibiting M2-type phenotype (CD11b+ F4/80+ Ly-6C- cells) are actively involved during pancreatic physiological development. In fact, these cells may be detected in the embryonic epithelial duct cells, and are involved in the development of human pancreas [50]. In addition, several observations showed that macrophages colonise the pancreatic islets, supporting the development of β-cell mass during embryonic state and after birth[51,52].

Due to both the protective and homeostatic effects that pancreatic macrophages may exert, similarly to resident macrophages in other tissues, islets macrophages adapt themselves to this specific environment [7,49] On the contrary, during T2D, under the effect of increased glucose concentrations, these M2-type cells switch to M1-type phenotype (CD11bhigh F4/80-/+Ly-6C+ cells) [53] which are characterized by an increased production of pro-inflammatory cytokines including IL-1β and higher expression of NLRP3-inflammasome [54,55]. Taken together, these data suggest that during T2D, the islets macrophage shifts towards M1-type thus supporting the inflammatory process inside the pancreatic islets [7,49,53].

Bimodal role of IL-1β in T2D

Despite evidence showing a pathogenic role of increased levels of IL-1β in suppressing the proliferation β-cells and their insulin secretion, the same cytokine, at lower concentrations may support the same cellular functions, suggesting a bimodal, dose-dependent effect [56,57]. The modulation of Fas inhibitor FADD-like interleukin-1-beta-converting enzyme (FLICE)-like inhibitory protein (FLIP) and the activation of protein kinase C signalling, by IL-1β,have been proposed to play a pivotal role in this setting. In fact, lower concentrations of IL-1β may increase FLIP expression; on the contrary, higher concentrations of IL-1β may suppress its expression, to β-cell apoptosis via Fas/Fas ligand pathway [58-61].

IL-1 blocking agents for T2D

Both preclinical and clinical observations reported the efficacy of IL-1 antagonism therapy in T2D [62,63]. Although IL-1 blocking agents seem to be ineffective in T1D patients [64], recent preclinical evidence showed an IL-1β-driven pro-apoptotic function on pancreatic β-cells, thus suggesting a potential role of IL-1β in the early phases of T1D pathogenesis [64]. In this context, it has been proposed that a combination approach with anti-IL-1 drugs, in the early phases of T1D, might be attractive, to block the local β-cell inflammation and apoptosis and to promote regulatory T-lymphocyte responses [62-64].

Anakinra is biologic drug antagonizing IL-1 activity and licensed for the treatment of RA and many auto-inflammatory disorders [33,65,66]. The possible therapeutic effect of Anakinra in T2D has been tested in a clinical trial in which 70 T2D patients were randomized to receive anakinra or placebo. Anakinra significantly decreased the glycated hemoglobin (HbA1c) levels and this result was associated with an increase of C-peptide secretion, after 13 weeks of treatment [67]. Furthermore, during the follow-up a reduction of the proinsulin/insulin ratio was observed after 39 weeks of anakinra withdrawal [68]. Further experiments, in animal models, confirmed that IL-1 antagonism was able to decrease inflammation in insulin sensitive tissues, and this result was associated with a reduction of macrophages infiltrates within the islet, leading to an improvement of β-cell function [69,70]. In addition, an improvement of the glucose disposition index, during oral glucose tolerance test, was observed during anakinra treatment, in obese human subjects without T2D [71]. In this context, a randomized clinical trial, enrolling patients with impaired glucose tolerance, recently reported a significant improvement, of both insulin secretion and insulinogenic index, after 4 weeks of anakinra. [72].

Gevokizumab, a recombinant humanized monoclonal antibody against IL-1β [73], was able to induce a decrease of HbA1c levels, associated with an increase of C-peptide secretion, as well a reduction of C-reactive protein in T2D patients, at the dosages of 0.03-0.1 mg/kg [74]. On the contrary, higher dosages did not show any therapeutic effect. To explain this apparent paradox, it has been supposed that at higher dosages, fully neutralizing the IL-1β activity, might deprive β cells of the physiologic stimulus that this cytokine plays, to support both insulin secretion and B cell proliferation, as we already discussed [56,57]. Canakinumab is a biological agent blocking IL-1β and was tested in a randomized clinical trial enrolling T2D patients. Fasting plasma glucose, insulin secretion rate and insulin levels were improved by canakinumab, after 4 week [75]. In addition, a large clinical trial is ongoing (ClinicalTrials.gov NCT01327846), in order to assess if Canakinumab treatment may decrease cardiovascular events, in T2D patients, via the improvement of insulin secretion and glycaemic parameters [76].

Expert commentary

Recently, the hypothesis that blocking IL-1 activity may be helpful in the treatment of RA-associated comorbidities, has been strongly emphasized [3]. This aspect is not merely a minor issue. At present, the costs of an appropriate RA therapy, although widely varies across Europe and worldwide, are alerting~~,~~ both the healthcare professionals and the designers of health policies, in order to achieve the best outcome at the lowest cost [77]. The 2 main RA comorbidities, cardiovascular involvement and T2D, are included among the most expensive clinical conditions in the developed world [4]. Thus, in this setting, targeting some molecule, whose therapeutic effects may extend beyond the joints inflammation ~~and~~ in order to control some comorbidity, is a strong perceived need [77], in those countries that are gradually reducing the health care budgets [4].

As we previously described, RA is characterized by synovial inflammation, joint destruction and systemic inflammation [13,14]. Intriguingly, in recent years many papers showed that the inflammatory molecules playing a pathogenic role in RA, are also involved in T2D [1-3], the latter, actually considered, an IL-1β inflammatory-mediated process (Figure 1). Of note, both preclinical and clinical observations reported the efficacy of IL-1 antagonism therapy in T2D [55,62]. On the contrary, despite experimental studies showed a possible role of TNF-α, in regulating insulin production and function, disappointing results were reported in the treatment of T2D patients with TNF-α inhibitors [1,63].

Recently, we demonstrated that different concentrations of glucose may influence the pro-inflammatory status of monocytes of RA patients. *In vitro* production of IL-1β from isolated human monocytes, obtained from RA and T2D patients, was enhanced after exposition to higher concentrations of glucose, and the highest levels of IL-1β were observed in patients affected by both RA and T2D [78]. In this experimental setting, a significantly higher expression of NLRP3-inflammasome was observed, after exposition to higher glucose levels, in isolated human monocytes, the highest expression observed in T2D/RA patients [78].

Furthermore, we showed that active RA patients, with concomitant T2D, treated with anakinra, reached the therapeutic targets of both the diseases [DAS28<2.6 and HbA1c <53mmol/mol, 7%], allowing us to taper or discontinue their antidiabetic therapy [79]. Finally, the results of a clinical trial enrolling RA patients, treated with anakinra, showed that the best responders to treatment were the patients affected by T2D comorbidity [80], confirming the synergistic effect of both the diseases in modulating the inflammatory status [3]. On these bases, an open, randomized, controlled, double-armed, multi-centre clinical trial is actually ongoing in Italy, whose primary end-point is the efficacy of anakinra in controlling signs and symptoms of T2D, in RA patients with concomitant T2D, (TRACK study, NCT02236481, www.clinicaltrial.gov).

Five-year view

Although in the past, the prevention of the joint destruction was strongly emphasized, now a great interest is focused to identify the best therapeutic choice to control the RA-associated comorbidities. Several data suggest that a large percentage of RA patients are affected by T2D, whose incidence has reached epidemic levels, in the developed countries, strongly increasing the health care costs. Thus, any strategy that may help the heath policies deciders to cut social costs, saving the quality of treatment is, at present, a strongly perceived need. To reach this goal, a better knowledge about the pathogenesis of these diseases as well as the possibility to treat different diseases with the same drug, may allow both policy designers and physicians to choose the most effective therapies, lowering the costs.

Key issues:

- Although in the past, the prevention of the joint destruction during RA was strongly emphasized, now a great interest is focused on associated comorbidities such as T2D.
- RA is an autoimmune disease in which IL-1β is a key component in the induction and progression of the disease, and therapies antagonizing its effects are effective in controlling the symptoms as well as the activity of RA.
- Many studies supported the pathogenic role of the IL-1β in T2D mirroring what has been observed in RA.
- The insulin deficiency, observed in T2D, is linked to different factors, such as lipotoxicity, glucotoxicity and amyloids deposits which are able to induce IL-1β overproduction.
- It has been reported that the increased concentrations of glucose may strongly influence the proinflammatory status of monocytes obtained from diabetic patients
- Both preclinical and clinical observations showed the efficacy of anti-IL-1 therapy in T2D .
- Clinical trials, enrolling RA patients with concomitant T2D, and designed to show if, anti-IL-1treatments may reach the therapeutic targets of both the diseases, are ongoing.
- A better knowledge about the pathogenesis of these diseases as well as the possibility to treat, in the same patient, different diseases with the same drug, may allow both policy designers and physicians to choose the most effective therapies, lowering the costs.

Declaration of Interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties

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*** Of considerable interest*

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