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18 Buisson, S. and Triebel, F. (2003) MHC class II engagement by several inflammatory diseases[3]. The RAGE–S100 interaction represents a novel proinflammatory axis involved in the expression of several cytokines, such as interleukin-1β and tumor necrosis factor-α (TNF-α). However, although blockage of RAGE–S100A12 suppresses the chronic cellular activation and tissue injury in various mouse models [3,8], there is one important gap: whether murine S100A12 exists is not yet known. Therefore, we performed a detailed computer analysis to identify the murine S100A12 gene.

The genes encoding 14 of the 21 members of the S100–calgranulins family are localised in a cluster on human chromosome 1q21 and several murine S100 homologues have been localised to a corresponding region on mouse chromosome 3 [9,10]. S100A8 and S100A9 are neighbouring genes in both mouse and human, and human S100A12 is localised in the S100 gene cluster between the S100A8 and S100A9 genes [10]. Like most other S100 genes, human S100A12 is composed of three exons and the protein is encoded by sequences in exons 2 and 3.

The University of California at Santa Cruz (UCSC) genome browser* [11] enabled us to compare the Feb. 2003 freeze of the murine genome with the Nov. 2002 assembly of the human genome. To search for the murine S100A12 gene, we inspected the murine sequence segment between S100A8 and S100A9, which are neighbour genes in both mouse and human, and human S100A12 is localised in the S100 gene cluster between the S100A8 and S100A9 genes [10]. Like most other S100 genes, human S100A12 is composed of three exons and the protein is encoded by sequences in exons 2 and 3.

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Absence of S100A12 in mouse: implications for RAGE–S100A12 interaction

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RAGE (receptor of advanced glycation endproducts), a member of the IgG superfamily, is present on numerous cell types, including monocytes, fibroblasts, endothelial and smooth muscle cells. Activation of the RAGE pathway is important in wound healing, atherogenesis, tumorigenesis, systemic amyloidosis and Alzheimer’s disease [1,2]. Ligation of RAGE activates multiple intracellular signaling pathways and several downstream signalling molecules have been identified [1]. RAGE also binds the non-AGEs (non-advanced glycation endproducts) S100B and S100A12, termed extracellular newly identified RAGE-binding proteins (EN-RAGEs) [3], and the RAGE–S100 interaction represents a novel proinflammatory axis involved in several inflammatory diseases [3].

Members of the S100–calgranulins family compose a multigenic family of non-ubiquitous cytoplasmic Ca2+-binding proteins of the EF-hand type, differentially expressed in a wide variety of cell types [4,5]. Some members, especially S100A8, S100A9 and S100A12 [6,7], are released from cells as a result of cellular activation. Secreted human S100A12 binds to RAGE on immune cells, promotes proliferation, induces the activation of NF-κB and the expression of several cytokines, such as interleukin-1α (IL-1α), IL-2 and tumor necrosis factor-α (TNF-α). However, although blockage of RAGE–S100A12 suppresses the chronic cellular activation and tissue

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and S100A9. The hits have the same order in both species and cover most of the murine segment. The murine sequence that triggers hit 9 is 60% identical to a region of the human S100A12 gene covering promoter, exon 1 and intron 1 (Figure 1). The corresponding regions of the S100A8 and S100A9 genes share a comparable degree of similarity between mouse and human arguing that hit 9 represents part of murine S100A12. However, analysing the murine sequence immediately following hit 9 we failed to detect exons 2 and 3. Instead, we found a region homologous to the human sequence near to the S100A9 locus, suggesting that the murine S100A12 exons 2 and 3 have been deleted. Furthermore, there is no evidence for a translocation in mouse because a search with the human sequence following intron 1 of the S100A12 gene did not trigger any homologous matches. There are no nearby sequencing gaps. Additional homology searches of all Jackson laboratory murine databases [13], using human S100A12 as the query, were futile. Moreover, a region homologous to the first exon of S100A12 is also present on the corresponding chromosome 2 of rat, however, exons 2 and 3 are again missing, suggesting that the S100A12 gene might be damaged in all rodents. However, the high conservation of the S100A12 gene during rodent evolution. The potentially deleterious A → G substitution in the putative TATA box of the murine S100A12 promoter (Figure 1) also points to an inactive evolutionary relic of a formerly active gene.

RAGE ligation by its various ligands has been implicated in various inflammatory-related diseases [1,2]. The hallmark of S100A12 is its accumulation at sites of acute and chronic inflammation and human S100A12 is undisputedly associated with inflammation [14]. Therefore, several proinflammatory properties of this protein might be caused by its binding to RAGE [3]. Thus, the RAGE–S100A12 interaction represents an attractive model to explain how RAGE and its proinflammatory ligand contribute to the pathophysiology of several inflammatory diseases [1,3]. Consequently, inhibition of the RAGE–S100A12 interaction could be considered as an attractive target for future therapies.

Figure 1. Hit 9 corresponds to the alignment shown, between the human sequence ranging from 14913088 to 149130541 base pairs on chromosome 1 (top) and murine sequence ranging from 91810347 to 91810828 base pairs on chromosome 3 (bottom). The alignment consists of 315 (60.9%) identical bases. Exon 1 of S100A12 is marked in red, and the putative TATA box is marked in green.
structural features and display sequence homology, there are obvious differences in biochemistry, distribution and expression. Definitive evidence for binding to RAGE has only been deduced for S100A12 and S100B [3]. Therefore, further investigations are required to analyse the molecular mechanisms by which soluble RAGE and anti-RAGE have beneficial effects on inflammation.

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TCR triggering: co-receptor-dependent or -independent?

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We wish to defend the kinetic-segregation (K-S) model of T-cell receptor (TCR) triggering [1,2] against several points raised by Trautmann and Randriamampita in their recent Opinion article on the initiation of TCR signalling [3]. The authors claim that the K-S model is weakened by apparently failing to account for co-receptor dependent signalling, is experimentally unsubstantiated and cannot explain the signalling effects of soluble MHC–peptide molecules.

It seems worth explaining why the K-S model was intentionally formulated without an obligatory role for co-receptors. At the time it was first proposed [1], the somewhat surprising view had emerged that TCR signalling was not invariably co-receptor dependent, as first vividly illustrated by the control of leishmaniasis by CD8+ Th cells in CD4-deficient mice [4]. Molecular analyses also indicated that TCR signals enhance the binding of CD8 to MHC class I [5] and of CD4 to the TCR [6]. Unexpectedly, the co-receptor function of CD4 was potentiated by removal of the kinase domain of CD4-associated p56lck and eliminated by inactivation of the Src homology 2 (SH2) domain from a kinase-inactive mutant [7]. Together, these observations suggested that, instead of TCR phosphorylation requiring CD4 or CD8 recruitment, co-receptor recruitment depended on prior phosphorylation of the TCR. Today, the observation that TCRs are triggered even when co-receptors are blocked hardly seems to warrant comment (see e.g. Ref. [8]).

The K-S model avoided an absolute requirement for co-receptors by allowing TCR phosphorylation (triggering) by free p56lck associated with the membrane inner leaflet (Figure 1). This does not mean that signalling is necessarily co-receptor independent, however. We initially envisaged that the co-receptors and other non-critical accessory molecules, such as CD2, might enhance signalling by stabilizing TCR–MHC–peptide complexes [1]. However, the extremely low affinities of co-receptor–ligand interactions make this unlikely [9]. Instead, co-receptors might stably recruit p56lck to incipiently phosphorylated TCRs through additional SH2 domain-dependent interactions, allowing the amplification of signalling beyond a critical threshold [9,10]. This might ensure that potent, cell-mobilizing co-receptor signalling is subservient to weaker, but fundamentally more important, TCR-derived signals.

Trautman and Randriamampita claim that there is little experimental support for the K-S model but this is not the case. Along with its compatibility with several long-standing features of TCR triggering [2],

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