Differential expression of CD150 (SLAM) on monocytes and macrophages in chronic inflammatory contexts: abundant in Crohn’s disease, but not in multiple sclerosis

Signalling lymphocytic activation molecule (SLAM, CD150), originally identified as a lymphocyte activation molecule, is now known to be expressed also on mature dendritic cells and on activated monocytes. Importantly, SLAM is distinct from other monocyte activation markers because its expression on monocytes is readily induced in vitro by bacteria derived ligands of Toll-like receptors (TLRs), and not by single stimulation with inflammatory cytokines. This study analysed SLAM expression on monocytes and macrophages in two distinct chronic inflammatory pathologies. In Crohn’s disease, the chronic inflammation in the gut is thought to result from inappropriate and ongoing activation of the mucosal immune system driven by the presence of normal luminal flora. The bacterial product flagellin has been suggested to be a dominant antigen in Crohn’s disease. Flagellin is the ligand for TLR5 and induces SLAM on monocytes. In contrast to Crohn’s disease, in multiple sclerosis (MS), the chronic inflammation in the central nervous system is commonly assumed not to be linked to bacterial infections, but rather is driven by autoreactive T cells that recognise self antigens. Frozen tissue sections from two normal colons, two normal ileums, colon specimens from two patients with Crohn’s disease, two lesions from one patient with MS (case 2 in Babbe and colleagues’), and three normal brains, were stained with the following monoclonal antibodies: anti-CD14–biotin (BMA Biomedicals, Augst, Switzerland), anti-SLAM (Kamiya Biomedical, Seattle, Washington, USA), and anti-CD68 (Dako, Hamburg, Germany). Considerable numbers of CD68+ macrophages and to a lesser extent CD14+ cells were present in the wall of the normal gut and in Peyer’s patches. SLAM+ cells were detected only in Peyer’s patches, and not in other parts of the normal tissue (not shown). Numerous CD14+ monocytes, CD68+ macrophages, and SLAM+ cells were detected throughout the inflamed gut of patients with Crohn’s disease (fig 1A–C). Some SLAM+ cells were round, but many had processes, indicating that they belonged to the monocyte/macrophage lineage (fig 1B). Double staining demonstrated SLAM expression on CD14+ monocytes and on CD68+ macrophages (fig 1D, E).

In normal brain specimens very few CD14+, CD68+, and SLAM+ cells were detected (not shown). The MS lesion was characterised by an active plaque and composed mainly of activated monocytes and macrophages (fig 2A, C, D). The CD68+ cells extended into the parenchyma and together with CD14+ cells surrounded the inflamed blood vessels, where only very few SLAM positive cells were detected (fig 2B, E). Thus, most, if not all, CD68+ and CD14+ cells did not express SLAM in this MS tissue lesion.

Figure 1 Expression of CD14, CD68, and SLAM in Crohn’s disease. Antibodies to (A) CD14, (B) SLAM, and (C) CD68 showed extensive accumulation of inflammatory cells in the mucosa of the gut. Elongated cells with processes were seen after staining for both CD14 and SLAM (arrows in A and B). Cell nuclei were counterstained with haematoxylin in A–C. (D) Immunohistochemical staining showing blue labelling of SLAM expressing cells and brown labelling of CD68 expressing cells. Two CD68+ cells coexpressing SLAM (arrow) and one cell expressing SLAM only (arrowhead) are labelled. (E) Double staining with anti-CD14 and anti-SLAM revealed cells that were positive for CD14 only (green), positive for SLAM only (red), and double positive (yellow). Original magnification: ×400 (A–C); ×1000 (D, E).
Further studies taking into account the pathological heterogeneity of MS are required to elaborate this. Thus, our study demonstrates for the first time the presence of SLAM+ monocytes and macrophages in a chronic inflammatory disease, Crohn’s disease. Furthermore, we show that this is not a feature common to all types of inflammation, because monocytes and macrophages did not express SLAM in the analysed MS lesions. The expression of SLAM on monocytes and macrophages in Crohn’s disease supports the concept that the inflammation in this disease is driven by bacteria derived TLR ligands.

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References


Multifocal microcarcinoid tumours in ulcerative colitis

I read with interest the report by Matsumoto and colleagues1 of a patient with ulcerative colitis and multiple microcarcinoid tumours, and would like to describe a similar recent case encountered in our department. A 44 year old man with an 18 year history of ulcerative colitis underwent total colectomy after a diagnosis of high grade dysplasia in a rectal biopsy. The resection specimen revealed a mucinous adenosarcoma of the rectum invading the submucosa, but not involving the muscularis propria, perirectal fat, or lymph nodes. There was also active ulcerative colitis of mild to moderate severity involving the distal 200 mm of the colon and rectum. The inflamed segment was extensively sampled and all sections showed multifocal endocrine cell proliferation within the muscularis mucosae and the superficial submucosa (fig 1). Most foci comprised clusters of between five and 50 cells, which were typically arranged in small nests and cords, but there were four larger endocrine cell aggregates from 1 to 2.5 mm maximum diameter. Some of the submucosal nests were closely apposed to nerves and ganglion cells. Immunohistochemistry on representative sections showed expression of cytokeratin, chromogranin, synaptophysin, and CD56 within the endocrine cells and close apposition to S100 protein positive nerves and dendritic cells. There was no evidence of endocrine cell hyperplasia within the overlying mucosa or in the normal proximal bowel.

Although there are several reports of neuroendocrine tumours arising in patients with inflammatory bowel disease, the finding

Figure 1  Endocrine cell proliferation within thickened rectal muscularis mucosae. There is no evidence of mucosal endocrine hyperplasia.
of microscopic and multifocal endocrine cell proliferations is much more rare. Indeed, the most appropriate terminology for these lesions is not clear. Matsumoto and colleagues used the term “microcarcinoids” to describe the endocrine proliferations in their patient. The lesions were described as “multiple small islands of cells” but the sizes of the lesions were not documented. Maruyama and colleagues described a non-colitic patient with multiple, variably sized endocrine cell proliferations and five typical grossly evident carcinoid tumours in the colon. They suggested that the microscopic lesions should be subdivided into microcarcinoids, endocrine cell microproliferations (ECMs), and transitional forms. The smaller ECMs and transitional lesions did not exhibit expansile growth or involving fibrous stroma. Abe et al., in describing a case of multiple duodenal endocrine cell proliferations, defined carcinoid tumours as greater than 5 mm diameter, microcarcinoids as between 0.5 and 2.9 mm, and lesions smaller than 0.5 mm (which they interpreted as hyperplastic) as “endocrine cell micronests”. According to these criteria, most of the lesions in our case would be classified as ECMs or micronests. Regardless of the terminology, it would appear that these cases show a spectrum of endocrine cell proliferation, but whether these are truly hyperplastic or neo-plastic is not clear.

As discussed by Matsumoto et al., it has been suggested previously that colonic endocrine cell hyperplasia in association with inflammatory bowel disease may represent a response to injury or inflammation. However, although this hypothesis may reasonably explain mucosal endocrine cell proliferation, the distribution of the lesions within the submucosa and muscularis mucosa in our patient and in some previous reports is less readily understood, particularly because the crypt endocrine population was not hyperplastic in these cases. Maruyama and colleagues noted in their case that the submucosal endocrine cells were often associated with ganglion cells and $100$ positive dendritic cells, and postulated that the proliferation involved a subpopulation of endocrine cells associated with submucosal nerve fibres. This suggestion is supported by the findings in our case. As noted by Matsumoto et al., deeply located endocrine cell proliferations are unlikely to be identified on endoscopic biopsies. Indeed, our patient underwent four colonoscopic examinations in the 12 months before surgery and no endocrine lesions were identified in a total of 24 biopsy samples examined during that period. Therefore, the incidence of such lesions may be underestimated, although whether this is a clinically relevant finding is not clear.

Authors’ reply

We appreciate the valuable comments regarding our case report published in the December 2003 issue of the journal. We are impressed by a similar case of ulcerative colitis complicating microcarcinoids described above.

As has been stated above, there are no established criteria that distinguish microcarcinoids from endocrine cell micronests (ECMs) occurring in the intestine. Thus, the terminology seems to be confused. However, the diagnosis of microcarcinoids in our case was based on the criteria for gastric carcinoids reported by Itsuno et al. For an analysis of autoimmune gastritis, Itsuno and colleagues defined microcarcinoids as lesions composed of endocrine cells over 0.5 mm, and ECMs as lesions between 0.1 and 0.5 mm in size. Because all the lesions in our case measured over 0.5 mm, and they consisted of crowding micronests, we judged them to be “microcarcinoids”. We apologise for the insufficient descriptions provided in our report.

Although such a distinction has not been shown to be appropriate for endocrine cell tumours in the large intestine, the application of the criteria seems to be reasonable, because ECMs and microcarcinoids in both autoimmune gastritis and ulcerative colitis are probably a consequence of chronic inflammation. The clinical relevance of the distinction of microcarcinoids from ECMs for the management of ulcerative colitis needs to be evaluated further.

As has been recommended, we performed immunostaining for S$100$ protein in the microcarcinoids of our case. However, the procedure failed to identify positive cells within the lesions. Thus, the association of nerve fibres is unlikely to explain the submucosal nature of the microcarcinoids in our case.

References


BOOK REVIEW

Molecular Biology and Pathology of Paediatric Cancer


The diagnosis of cancer, especially in children, has evolved into a multistep process involving many diagnostic techniques. Molecular techniques are now essential tools in the diagnosis of paediatric cancer. This book will update pathologists and clinicians on the current techniques and their application to pathological diagnosis.

The first introductory chapter gives an excellent overview of childhood cancer including patient management. This is followed by two sections, the first covering laboratory methods and techniques. Also included in the first section is a chapter on “familial and predisposition syndromes”, which includes disorders of DNA repair and familial cancer syndromes. The second section consists of 12 chapters, which deal mainly with the molecular pathology of the major paediatric cancers, but also include information on the clinical features, pathology, and prognosis of selected neoplasms. The text is well written and complemented by appropriate tables and figures.

A typographical error appears in tables 1.5 and 1.2. Both tables list 11q13, instead of the correct 11p13, in the translocation for desmoplastic small round cell tumour.

I thoroughly enjoyed reading this book. I think that it is an excellent book in its category and would recommend it to scientists, clinicians, and pathologists who wish to understand the recent developments in paediatric cancer diagnosis.

D Govender

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