Cellular & Molecular Immunology (2010) 7, 100–103

www.nature.com/cmi

MINI REVIEW

CD24: from A to Z

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As a testament to the importance of CD24, researchers with diverse interests, including adaptive immunity, inflammation, autoimmune diseases and cancer, have encountered CD24. CD24 is overexpressed in many cancers and appears oncogenic. In the adaptive immune response, CD24 is a redundant costimulatory molecule in costimulation-rich lymphoid organs but is essential in selected target organs tested, such as brain and skin. More recent studies suggest it may have a role in discriminating danger and pathogen-associated molecular patterns by dendritic cells. The biology of CD24 is intriguing but poorly understood. Here we summarize the major findings associated with CD24 to stimulate new ideas for further research that may reveal the underlying link among the diverse processes mediated by CD24.
Cellular & Molecular Immunology (2010) **7,** 100–103; doi:10.1038/cmi.2009.119

Keywords: autoimmune disease; cancer; CD24; inflammation

INTRODUCTION

The heat-stable antigen (mouse CD24) was identified 30 years ago.[1] Since then, CD24 has been extensively used as a marker for the differentiation of hematopoietic and neuronal cells, in addition to tissue and tumor stem cells. Corresponding to its wide distribution and highly variable glycosylation, an apparently unrelated and diverse array of functions has been attributed to CD24. In this paper, we will provide a brief summary of the roles for CD24 in adaptive immunity, inflammation, autoimmunity and cancer.

THE GENE, THE GLYCOPROTEIN AND THE PARTNERS

CD24 was first identified in 1978 when Springer produced xenogenic rat antimouse antibodies M1/69 and M1/75, and due to its heat resistance, he called it the heat-stable antigen.[1] In 1990, mouse Cd24 gene was cloned and found to encode a small protein whose mature form consists of only 27 amino acids.[2] Soon after, the human *CD24* gene was identified.[3] Human *CD24* is located on chromosome 6q21, as determined by *in situ* hybridization.[4] Three intronless CD24 pseudogenes, located on chromosomes 1, 15 and Y, were also identified.[4] The mouse *Cd24* gene was mapped to chromosome 10.[5] It was originally called *Cd24a* to distinguish it from intronless retroposons mapped to mouse chromosomes 8 and 14.[5] Since the retroposons were not expressed, the term *Cd24a* is no longer widely used. Mouse *Cd24* cDNA consists of a short open-reading frame (231 bp) and a long 3′ untranslated region (UTR) (1.5 kb), which was shown to have an important role in *Cd24* mRNA stability.[6] Similarly, human *CD24* cDNA has a 0.24-kb open-reading frame and 1.8 kb 3′ UTR, and the UTR region dinucleotide deletion can affect *CD24* mRNA stability.[7] The primary structure of both mouse and human CD24 shows multiple *N*- or *O*-glycosylation sites. The human CD24 molecule has additional serine and threonine residues, rendering the molecule like a mucin.[3] CD24 protein isolated from different tissues or cell types has different molecular weights, ranging from 20 to 70 kd,[3,8–10] demonstrating that the glycosylation of heat-stable antigen and CD24 is highly variable and cell-type dependent. The saccharide structure of CD24 from mouse brain is now being elucidated.[11,12]

Several ligands of CD24 have been identified, and ligand specificity seems to be dependent on cellular context because of the highly variable glycosylation of CD24. For instance, CD24 can promote cancer-cell rolling and colonization to lung only when fucose transferase VII converts CD24 into a P-selectin ligand.[13–16] In brain, CD171 (also known as L1) is a receptor for 2,3-linked sialic acid on CD24, whereas TAG-1 and Contactin are receptors for Lewis^X on CD24. All of these ligands mediate CD24-induced inhibition of neural growth.[17–19] In hematopoietic cells, CD24 is known to bind to molecules exhibiting danger-associated molecular patterns (DAMPs). Additionally, CD24, DAMPs and Siglec G (mouse) or Signlec 10 (human) form a trimolecular complex.[20] As a glycosyl phosphatidylinositol-anchor molecule, CD24 mediates signal transduction by recruiting Src family protein tyrosine kinases (PTKs) including c-fgr, lyn and lck via membrane rafts, and activates the mitogen-activated protein kinase pathway, which involves B- and T-cell development and apoptosis, cell binding and granulocyte oxidative burst.[21–28]

BROAD EXPRESSION AND DIVERSE FUNCTIONS FOR ADAPTIVE IMMUNE RESPONSE

CD24 is expressed on hematopoietic cells, including B cells,[3,8,29–32] T cells,[33–37] neutrophils,[37,38] eosinophils,[39] dendritic cells[36,40,41] and macrophages,[42] as well as on non-hematopoietic cells, including neural cells,[10,43–46] ganglion cells,[47,48] epithelia cells,[49–52] keratinocyte,[53] muscle cells,[54,55] pancreas,[56,57] epithelial stem cells[58,59] and many types of cancer cells.[60] As a rule, CD24 tends to be expressed at higher levels in progenitor cells and metabolically active cells and to a lesser extent in terminally differentiated cells. The function of CD24

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Received 8 November 2009; revised 13 December 2009; accepted 16 December 2009

is unclear for most cell types; however, diverse immunological functions for CD24 have been reported.

CD24 is expressed at high levels on B-cell progenitors and remains expressed on mature resting B cells but not on terminally differentiated plasma cells.[61] CD24-deficiency resulted in a reduction in late pre-B and immature B-cell populations in the bone marrow.[62–64] On activated B cells, CD24 functions as a T-cell costimulator for CD4 T-cell clonal expansion.[35,65] Likewise, CD24 is highly expressed on immature T cells and weakly expressed on peripheral T cells,[34] but it is upregulated in activated T cells.[35] A functional CD24 gene is required for optimal homeostatic proliferation of T cells in a lymphopenic host.[36] Interestingly, on dendritic cells, CD24 is a negative regulator for T-cell homeostatic proliferation.[66] At the organismal level, CD24 deficiency synergizes with CD28 deficiency in suppressing both CD4 and CD8 T-cell responses.[67,68] Moreover, CD24 deficiency increases the efficiency of clonal deletion.[69]

CD24 AND AUTOIMMUNE DISEASE

The first evidence linking CD24 to autoimmune disease was reported 10 years ago when CD24-deficient mice were found to be highly resistant to experimental autoimmune encephalomyelitis.[70] Adoptive transfer studies revealed a critical role for CD24 on both T cells and radio-resistant host cells.[70,71] Furthermore, although pathogenic T cells can be recruited at comparable efficiency to the central nervous system of both wild-type and CD24-deficient mice, the T cells persist and expand only in the wild-type central nervous system. *In vitro* experiments demonstrated that the costimulatory activity of microglia and astrocytes from CD24-deficient mice is reduced. These data suggest that CD24 expressed on microglia and astrocytes may promote the activation and proliferation of pathogenic T cells.[71] Using transgenic mice with a glia-specific promoter, overexpression of CD24 in the central nervous system led to a more severe and progressive disease EAE.[72] The essential role of CD24 expression on T cells in experimental autoimmune encephalomyelitis is not understood. Apart from experimental autoimmune encephalomyelitis, CD24 deficiency also protected mice against experimental autoimmune thyroiditis.[73]

The relationship between CD24 and autoimmune disease is supported by clinical data. Polymorphisms of CD24 are associated with the risk and the progression of autoimmune diseases, including multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus (SLE). The CD24 gene has an SNP (P170) that has a nonconservative replacement in the C-terminus of the mature protein, either Alanine (A, $P170^{C}$) or Valine (A, $P170^{T}$). Zhou *et al.*, first reported that the $CD24^{V/V}$ associated with the risk and progression of multiple sclerosis, and the expression of CD24 on peripheral blood T cells of $CD24^{V/V}$ patients, was higher than that of $CD24^{A/A}$ genotype patients.[74] The association was confirmed in a Spanish cohort,[75] although another group reported contradictory data from two cohorts.[76] For SLE, Sanchez *et al.* studied three cohorts of Caucasian patients and controls that included Spanish, German and Swedish patients and reported that the frequency of the $CD24^{V/V}$ genotype was higher than the controls in the SLE patients in the Spanish cohort but not in the German or Swedish cohorts.[77] By screening more than 1000 rheumatoid arthritis patients and 800 healthy individuals, they also found that the $CD24^{V/V}$ genotype was more common among rheumatoid arthritis patients;[78] a similar association was reported for giant cell arthritis.[79] The other three polymorphisms are found in CD24 mRNA long 3′ UTR, including P1056, P1527 and P1626. Among them, the dinucleotide deletion of P1527 can destabilize CD24 mRNA. Importantly, the dinucleotide deletion conferred protection against multiple sclerosis and SLE.[7]

The mechanism by which CD24 regulates autoimmune disease remains to be fully elucidated. Apart from its costimulatory activity, CD24 is a genetic check point in T-cell homeostatic proliferation in lymphopenic hosts. Lymphopenia, which is the underlying cause of T-cell homeostatic proliferation, is a common phenomenon in autoimmune disease. CD24 expressed on T cells was found to be essential for T-cell homeostatic proliferation.[36] Furthermore, because CD24 regulates the efficacy of clonal deletion,[69] it can be envisioned that mice with a targeted mutation of CD24 may have a smaller burden of high-affinity autoreactive T cells.

CD24 IN INFLAMMATION: DISCRIMINATING DANGER AND PATHOGEN-ASSOCIATED MOLECULAR PATTERNS

Inflammation is an innate immune response to infection and tissue injury.[80] The inducers of inflammation can be classified into two categories. The first and the most potent are pathogen-associated molecular patterns,[81] and the second, of lesser importance, are DAMPs.[82] Interestingly, CD24 was recently demonstrated to be associated with a variety of DAMPs, such as high mobility group box protein 1, Heat-shock proteins and nucleolins.[20] Through its interaction with SiglecG (mouse) or Siglec10 (human), CD24 selectively represses the host response to tissue injury. Since the pathway does not affect the host response to pathogen-associated molecular patterns, it has recently been proposed that the CD24–SiglecG pathway discriminates DAMPs from pathogen-associated molecular patterns.[83] This pathway may contribute to the cancer immune escape hypothesis, and dysfunction in this pathway might contribute to the etiology of autoimmune disease.

CD24 IN CANCER CELLS

CD24 is broadly overexpressed on many types of tumor tissues,[60,84] including B-cell lymphomas,[85] erythroleukemia,[22] gliomas,[86] small cell lung cancer,[87] esophageal squamous cell carcinoma,[88] hepatocellular carcinoma,[89] cholangiocarcinoma,[90,91] pancreatic adenocarcinoma,[92] urothelial carcinoma,[93,94] ovarian cancer,[95] breast cancer,[28,96,97] primary neuroendocrine carcinomas[98] and prostate carcinomas.[99] Human cancer stem cells appear to have decreased expression of CD24 compared to their offspring;[100,101] however, it is unclear if the same pattern holds in mice.

CD24 is an import marker for cancer diagnosis and prognosis. In breast cancer, CD24 expression is significantly higher in invasive carcinoma than in precancerous lesions. Cell-surface and cytoplasmic expression of CD24 correlates to poor prognosis, histology grades, tumor sizes and lymph node positivity.[96,97] In non-small cell lung cancer, CD24 expression is an independent marker for the overall survival of cancer patients.[102] Moreover, in esophageal squamous cell carcinoma, CD24 expression correlates with tumor lymph node metastasis, tumor grade and survival time.[88] Similar observations were found in many types of cancer, including cholangiocarcinoma,[90,91] urothelial carcinoma,[93,94] ovarian cancer[95] and prostate carcinomas.[99] Consistent with a causative role for CD24 in cancer pathogenesis, small-interfering RNA silencing of tumor cell CD24 expression had a direct effect on tumor cell proliferation and survival in tissue culture.[103] Antibody-blocking experiments show that anti-CD24 monoclonal antibody can inhibit the growth of human pancreatic cell lines *in vitro*.[92] Importantly, targeted mutation of CD24 significantly reduced the size of hepatocellular carcinomas induced by the transgenic expression of hepatitis virus B genes.[104] However, additional studies are needed to demonstrate the function of CD24 in cancer pathogenesis and the underlying mechanisms involved.

CONCLUDING REMARKS

Many scientists have encountered CD24 in their research, but few have dwelled on its importance. Through our brief summary of CD24, in apparently different biological and pathological processes, we wish to stimulate increased awareness of this tiny gene that encodes a glycoprotein of 27–30 amino acids. Are the apparently diverse functions a mere reflection of its structural variations caused by differential glycosylation? If there is a biological process regulated by CD24 that impacts the immune response, inflammation, autoimmune diseases and cancer biology, only time and experimentation will tell.

ACKNOWLEDGEMENTS

This work is supported by grants from the Chinese Natural Science Foundation, US National Institute of Health and US Department of Defense.

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