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DOI:

[10.1016/j.biocel.2017.05.025](https://doi.org/10.1016/j.biocel.2017.05.025)

*Document Version*

Publisher's PDF, also known as Version of record

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*Citation for published version (APA):*

Ortiz-Zapater, E., Santis, G., & Parsons, M. (2017). CAR: A key regulator of adhesion and inflammation. *The international journal of biochemistry & cell biology*, 89, 1-5. <https://doi.org/10.1016/j.biocel.2017.05.025>

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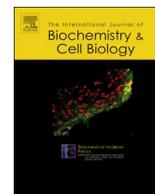
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## Molecules in focus

## CAR: A key regulator of adhesion and inflammation

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## ARTICLE INFO

## Keywords:

Coxsackievirus adenovirus receptor

Cell-cell adhesion

Transmigration

Cancer

Inflammation

## ABSTRACT

The coxsackie and adenovirus receptor (CAR) is a transmembrane receptor that plays a key role in controlling adhesion between adjacent epithelial cells. CAR is highly expressed in epithelial cells and was originally identified as a primary receptor for adenovirus cell binding. However, studies over the last 10 years have demonstrated that CAR plays a key role in co-ordinating cell–cell adhesion under homeostatic conditions including neuronal and cardiac development and cell junction stability; it has also been implicated in pathological states such as cancer growth and leukocyte transmigration during inflammation. Here we provide an overview of the functions of CAR as an adhesion molecule and highlight the emerging important role for CAR in controlling both recruitment of immune cells and in tumorigenesis.

## 1. Introduction

The Coxsackie and adenovirus receptor CXADR or CAR, also known as CAR-like membrane protein (CLMP) was first identified as a high-affinity receptor for the coxsackie B virus and adenovirus (Ad) serotypes 2 and 5 (Bergelson et al., 1997) and was subsequently shown to belong to the Junction Adhesion Molecule (JAM) family within the immunoglobulin (Ig) superfamily (IgSF) of proteins that localise in tight junctions and along the lateral membrane of epithelial cells (Coyné and Bergelson, 2005). JAM proteins are also found in intercellular junctions of endothelial cells and on the surface of leukocytes, platelets and erythrocytes (Luissint et al., 2014). JAM proteins have been implicated in a diverse array of functions involving cell–cell adhesion including barrier function, leukocyte migration, platelet activation angiogenesis and reovirus binding (Garrido-Urbani et al., 2014). JAMs are type I transmembrane glycoproteins, composed of two extracellular Ig-like domains, one transmembrane domain and one cytoplasmic tail of variable length containing a PDZ domain. The Ig domains allow for both homo and heterodimerisation in *trans*. The JAM family include a distinct group sometimes referred to as the “classical” JAM proteins that comprises: JAM-A, JAM-B and JAM-C. CAR, Endothelial Selective Adhesion Molecule (ESAM), JAM-L and JAM-4 make up a separate subfamily and have longer cytoplasmic tails. JAMs associate with adaptor/signalling proteins through the PDZ domain in the C-terminus and homo or hetero-dimerize with other JAMs via the extracellular domain (Garrido-Urbani et al., 2014).

## 2. Structure of CAR

The murine and human CAR genes are composed of 8 exons and are located on the chromosome 16 and chromosome 21 (21q21.1), respectively, from which different isoforms are generated by alternative splicing (Matthaus et al., 2016). Its predominant isoform, found at the cell membrane is a 346 amino acid, 46 kDa transmembrane protein. The structure of CAR comprises an extracellular domain, a transmembrane region and an approximately 15 kDa cytoplasmic tail (Fig. 1A); (Cohen et al., 2001). As with other members of the JAM family, the extracellular domain is made up of two Ig components: the N-terminal located domain belongs to the V-subtype of Ig domains (referred as D1) and is connected to the membrane proximal Ig domain of the C2-type Ig domain, referred to as D2. Both domains are connected by a short linker, which is proposed to potentially provide flexibility in the extracellular part of the protein, and contain glycosylation and palmitoylation sites which are thought to regulate the function of CAR (Excoffon et al., 2007). Cysteines 259 and 260 within the cytoplasmic domain of CAR are palmitoylation sites and are responsible for CAR localisation at the plasma membrane (van't Hof and Crystal, 2002). Studies using truncation mutants of CAR have shown that amino acids 261–315, which contain the tyrosine/threonine/serine phosphorylation sites, are required to both enable calyculin-driven phosphorylation of CAR and activate p44/42 in response to homo-dimerisation in *trans* (Farmer et al., 2009; Morton et al., 2013). Furthermore, two serine/threonine (290/293) phosphorylation sites have been shown to influence CAR mediated endocytosis of E-cadherin (Morton et al., 2013). In addition to this, the cytoplasmic tail contains one postulated

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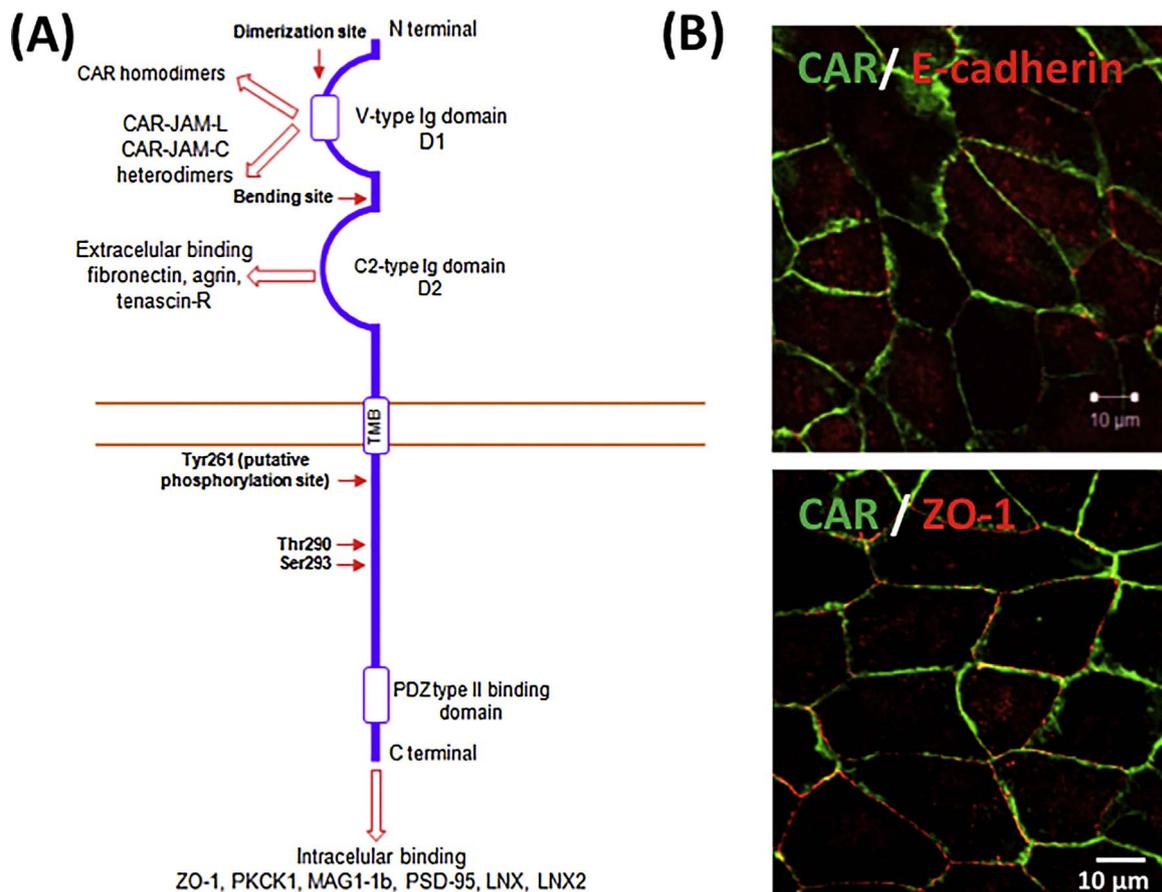


Fig. 1. CAR function and localisation.

(A) Schematic representation of CAR and associated binding partners (B) Confocal images of Human Bronchial Epithelial Cells (HBEC) overexpressing CAR-GFP and stained with E-cadherin (upper panel) and ZO-1 (bottom panel).

tyrosine phosphorylation site although to date this remains unexplored in the function of CAR (Fig. 1A).

CAR is able to homodimerise through its IgG like domains. In crystals, the extracellular region of CAR forms U-shaped homodimers through the binding of their D1 domains (Matthaus et al., 2016). Although initial studies suggested that the membrane-proximal D2 Ig domain might not be necessary for correct adenovirus binding or homodimer formation, further biochemical binding and adhesion studies suggest that the interaction between D1 and D2 domains are implicated in homophilic interactions. It is thought that trans-homophilic interaction may be initiated by CAR monomers from opposing cells via through the D1-D1 interface. CAR mediated adhesion could then be further strengthened by a change in the conformation which relocates the Ig domains in a manner in which they bind by forming D1-D2 interfaces in a linear arrangement (Matthaus et al., 2016; Patzke et al., 2010).

Aside from these homophilic interactions, CAR is able to heterodimerise with both extracellular and intracellular molecules. CAR binding with extracellular matrix proteins such as fibronectin, agrin or tenascin-R has been observed to occur via the CAR D2 domains (Matthaus et al., 2016). CAR can also interact with JAM-C and JAM-L (Garrido-Urbani et al., 2014). CAR and JAM-L interaction is thought to have an immune regulatory role in the activation of T-cells (Verdino and Wilson, 2011).  $\gamma$ d T-cells express JAM-L on their surface and upon binding of CAR, signalling pathways are activated, including the phosphoinositide-3-kinase (PI-3-K) pathway, leading to cell proliferation and cytokine production (Verdino et al., 2010). The C-terminal PDZ intracellular binding domain is also important in CAR function at the cell membrane, as it enables it to bind to multiple other structural proteins, including ZO-1 (Zona occludens-1), membrane-associated

guanylate kinase 1b (MAGI-1b), protein interacting with protein C kinase (PICK1), postsynaptic density 95 (PSD-95), Ligand of-Numb protein-X (LNX) and LNX2 (Garrido-Urbani et al., 2014). All these interactions between CAR and intracellular proteins suggests that CAR is present in the plasma membrane in multiple protein complexes and highlights its importance in regulating epithelial homeostasis. In support of this, phosphorylation of CAR in human epithelial cells play a key role in determining epithelial cell adhesion through control of E-cadherin stability at cell-cell junctions (Hussain et al., 2011; Morton et al., 2013).

### 3. Expression and activation

CAR is expressed and regulated in many organs including brain, heart, lung, liver, testis, pancreas or kidney (Matthaus et al., 2016). CAR expression levels change during embryonic development and the importance of this has been highlighted by the fact that deletion of CAR in the mouse leads to an embryonic lethal phenotype at days 11.5–13.5 due of malformation of the heart and haemorrhage (Dorner et al., 2005). CAR deficient embryos demonstrate impaired lymphatic endothelial cell adhesion, which impairs the separation of blood and lymphatic vessels (Mirza et al., 2012). CAR is also strongly expressed the neural tube and from E10.5, throughout the brain (Patzke et al., 2010). CAR conditional knockout adult mice have dilated intestinal tract, atrophy of the exocrine pancreas, complete atrio-ventricular block and abnormal thymopoiesis (Pazirandeh et al., 2011). These mice also show disrupted intercellular contacts in the myocardium with altered localization of connexin 45,  $\beta$ -catenin and ZO-1 preceding cardiac dysfunction (Lim et al., 2008). CAR expression is also abundant in axon tracks throughout the adult brain, at the presynapse in some

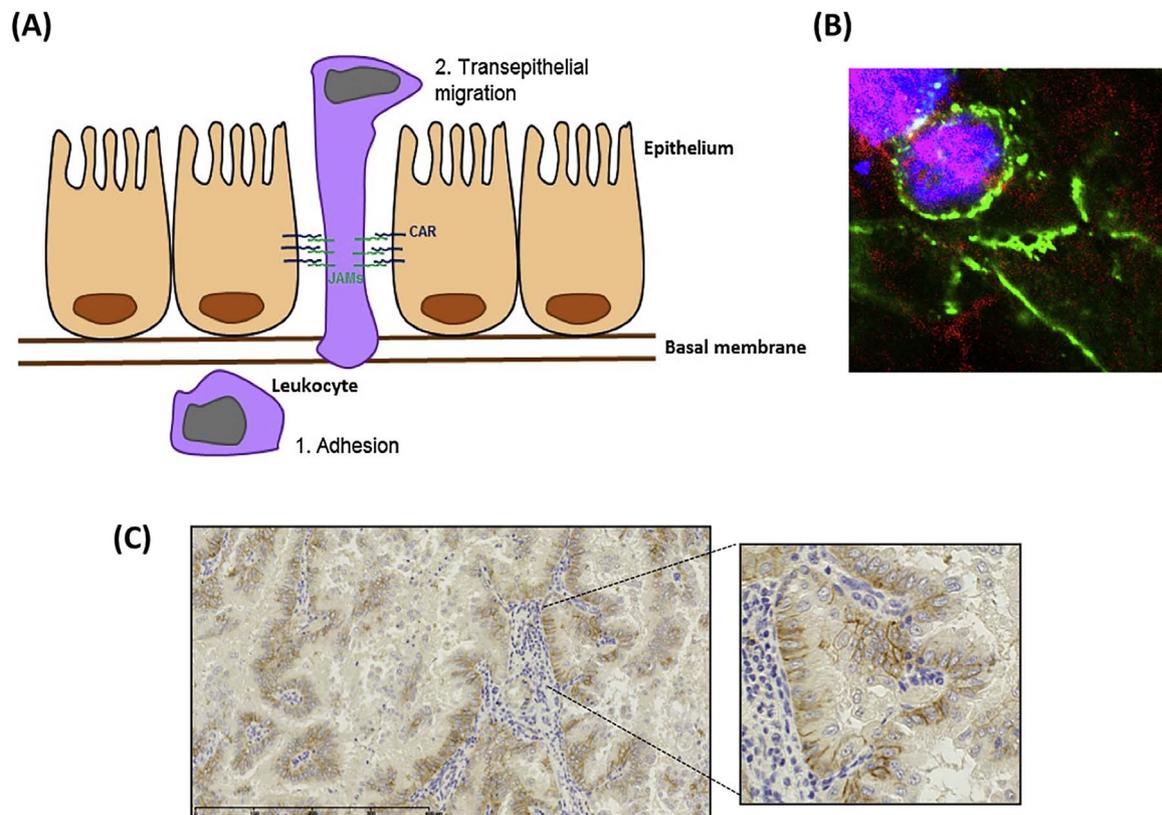


Fig. 2. Functions of CAR in disease.

(A) Diagrammatic representation of the role of CAR in trans-epithelial migration. Leukocytes adhere to the basolateral side of the epithelium before trans-epithelial migration along the basolateral membrane. Adhesion molecules such as JAMs and CAR promote this migration (adapted from Garrido-Urbani et al., 2014). (B) Confocal image of THP-1 cells undergoing trans-epithelial migration. THP-1 human monocytes cells were added to confluent monolayers of HBEC and fixed after 24 h. THP-1 cells are shown in blue, HBEC cells expressing CAR-GFP are shown in green and actin in red. Note clustered CAR around the THP1 cell. (C) CAR expression determined by immunohistochemistry in formalin-fixed paraffin-embedded section a human lung adenocarcinoma tissue. Panel on right shows zoom of denoted area.

mature neurons, and recruited to activated presynapses. Genetic deletion of CAR in the mouse brain affects adult neurogenesis, synaptic function, and behaviour (Zussy et al., 2016). These findings underline the importance of CAR in regulating multiple different types of cell–cell interactions and suggest a key regulatory role of this receptor in mediating dynamic cell adhesion processes during development and homeostasis.

CAR has a role in the dynamic control and regulation of epithelial cell junction formation and stability through homodimerisation *in trans* with the extracellular D1 domains of other CAR proteins in adjacent cells. CAR overexpression in CHO cells has been shown to limit the passage of ions and macromolecules across the epithelium and treatment of cells with soluble CAR ectodomain disrupts tight junction formation due to competitive binding across two adjacent membranes, suggesting strengthening of tight junctions by CAR homodimerisation *in trans* (Cohen et al., 2001). However, this role for CAR appears to potentially be organ specific as increased permeability in the heart but not in the gut of mice (Pazirandeh et al., 2011). CAR has been shown to interact directly with scaffolding proteins present in tight junctions, specifically ZO-1 and Multi-PDZ Domain Protein-1 (MUPP1) (Cohen et al., 2001). Both of these scaffolding proteins bind to F-actin, therefore the interaction of CAR with these two proteins implicates CAR in the potential co-ordination of cytoskeletal dynamics. Indeed, CAR has been shown to interact and contribute to F-actin bundling in neurons and has additionally been suggested to associate with the F-actin regulatory molecule Rho Kinase (ROCK) (Saito et al., 2014). CAR has also been shown to regulate migration in U87 glioma cells via the binding of tubulin to the cytoplasmic tail of CAR (Fok et al., 2007).

In addition to roles within the tight junction, basolateral localisation of CAR at cell–cell adhesion sites has been demonstrated in both airway

epithelial cells and cardiomyocytes, and co-localisation of CAR and N-Cadherin has also been observed in Sertoli cells (Wang et al., 2007). Cardiac myocytes overexpressing CAR also show severely disrupted adherens junctions *in vivo*, resulting in cardiomyopathy (Caruso et al., 2010). Moreover, CAR overexpression destabilises junctional E-Cadherin in bronchial epithelial cells by promoting endocytosis of E-Cadherin (Morton et al., 2013). The presence of Ad also affects E-Cadherin dynamics; this is mediated by CAR clustering and subsequent binding of  $\beta$ -catenin to disrupt E-Cadherin localisation (Hussain et al., 2011). These findings combined demonstrate that CAR can act at a number of different points to regulate cell–cell adhesion integrity and this occurs through direct or indirect effects on the actin cytoskeleton. The precise mechanisms by which CAR co-ordinates these events remain to be fully explored (see Fig. 1B).

#### 4. Biological functions in inflammation

In addition to controlling cell–cell adhesion integrity in homeostasis, CAR is emerging as an important player in the control of inflammation. CAR expression is upregulated in rat cardiomyocytes in chronic autoimmune inflammatory conditions (Ito et al., 2000). However, CAR expression on normal human bronchial epithelial cells or A549 lung epithelial cells is unaffected by cytokine treatments (Vincent et al., 2004). Recent work has also shown that epithelial cells from patients with cystic fibrosis express CAR at higher levels compared with healthy donor cells, which leads to increased infectivity with Ad (Sharma et al., 2017). We have also recently shown that CAR is hyperphosphorylated *in vivo* in both acute and chronic lung inflammation models but that CAR expression levels remain unchanged (Morton et al., 2016). Conversely, CAR expression is decreased in primary

cultures of murine hippocampal neurons and adult murine neural progenitor cells when incubated with TNF $\alpha$  and IFN- $\gamma$  in a dose-dependent manner. Similarly, a pro-inflammatory environment induced by Alzheimer disease and/or systemic inflammation is associated with CAR loss in the hippocampus (Zussy et al., 2016). These apparently conflicting findings suggest that tissue-specific regulation of CAR transcription and post-translational modification may be dependent upon the local immune cell populations that have yet to be precisely characterised.

CAR interactions with other members of the JAM family are a potential mechanism by which CAR may contribute to control of local immune responses. CAR expressed on skin epithelial cell membranes binds to JAM-L on  $\gamma\delta$  T cells (Verdino et al., 2010). This interaction also occurs between CAR on gut epithelial cells and JAM-L on neutrophils (Zen et al., 2005). Similarly, have demonstrated that *in trans* homodimers of CAR within epithelial cell–cell adhesions are phosphorylated in response to exogenous TNF $\alpha$  and that this contributes to efficient transmigration of monocytes and neutrophils, both *in vitro* and *in vivo*, suggesting that CAR may be an important receptor in the control of inflammation (Morton et al., 2016). As neutrophils and T cells play a role in host immunity, these data suggest that CAR may be ideally positioned to modulate the immune response from the epithelial or endothelial cell compartments. Further work is needed to define the mechanisms by which CAR-dependent co-ordination of immune cell adhesion and transmigration occurs, as well as potential roles for CAR in different pathological immune responses *in vivo* (see Fig. 2A and B).

## 5. Potential medical relevance

In addition playing a role in inflammation and autoimmune diseases, CAR has also been described to contribute to cancer progression (Fig. 2C). The role of CAR in tumorigenesis has been largely been suggested to cell–cell adhesion. In that sense, CAR expression is downregulated in parotid glands, colon cancer, prostate cancers and bladder cancer cells whilst increased CAR expression has been reported in cervical, ovarian and glioblastoma cancer cell lines (Reeh et al., 2013). Using a multi-tumour array analysis, Reeh et al. showed a significant increased CAR levels at the tissue level in comparison to healthy patients in basalioma, larynx carcinoma, Warthin's tumour, lung, cervical, endometrial, ovarian and bladder cancer, thyroid adenoma, carcinoma and neuroblastoma. Conversely, a decrease in CAR expression was seen in pleomorphic adenoma of the parotid gland, colon and prostate cancer, as well as subtypes of renal cell cancers (Reeh et al., 2013). Differences in CAR expression were observed at different stages of malignancy, indicating the protein expression is either increased or lost as the disease progresses (Reeh et al., 2013). The variability in CAR expression among different cancer types may be due to pre-existing endogenous levels of CAR expression within these different tissues.

CAR has also been shown to have both tumour suppressor and promoting functions, depending on the type of cancer. For example, in both bladder cancer the overexpression of CAR decreases cell growth *in vitro* and in gastric cancer cells the depletion of CAR increases migration, proliferation and invasion (Anders et al., 2009). By contrast, reduction of CAR resulted in reduced cell growth in oral squamous carcinoma and in colony formation, adhesion, transwell migration and xenograft tumorigenesis in lung cancer cell lines (Saito et al., 2014). CAR expression correlates with the expression of mesenchymal markers, suggesting a potential role in Epithelial to Mesenchymal transition (EMT) (Zhang et al., 2012). Finally, CAR expression has been associated with cancer stem cell phenotype. CAR overexpressing cells are more resistant to paclitaxel and radiation, self-renewing, and more tumorigenic than parental cells and the siRNA depletion of CAR inhibits these functions (Zhang et al., 2012). This highlights the potential of CAR in tumour progression, although the mechanism of how CAR mediates these phenotypes remains poorly defined.

CAR is now a well-recognised key mediator of cell–cell adhesion in a range of different tissues and even though a number of the precise mechanistic pathways remain poorly understood, it is clear that CAR can regulate junction dynamics through association with adaptor proteins, cytoskeletal remodelling and additional indirect signalling pathways. Expression of CAR in cancer cells contributes to tumour growth and as CAR has been shown to be an important receptor in the control of inflammation, this raises the possibility that CAR may also act on immune cell infiltration into tumours. Although the mechanisms by which CAR operates within these different disease settings remains unclear, given the restricted expression of CAR in adult tissues and the altered regulation in disease, we propose that CAR represents a potentially important therapeutic target in inflammatory disease and in cancer.

## Acknowledgments

The authors acknowledge funding from King's Health Partners, National Institute for Health Research (NIHR) Clinical Research Facility and NIHR Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust, King's College London.

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