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Review article

Caveolae create local signalling domains through their distinct protein content, lipid profile and morphology

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ABSTRACT

Compartmentation of signalling allows multiple stimuli to achieve diverse cellular responses with only a limited pool of second messengers. This spatial control of signalling is achieved, in part, by cellular structures which bring together elements of a particular cascade. One such structure is the caveola, a flask-shaped lipid raft. Caveolae are well-recognised as signalosomes, platforms for assembly of signalling complexes of receptors, effectors and their targets, which can facilitate efficient and specific cellular responses. Here we extend this simple model and present evidence to show how the protein and lipid profiles of caveolae, as well as their characteristic morphology, define their roles in creating local signalling domains in the cardiac myocyte. This article is part of a Special Issue entitled "Local Signaling in Myocytes."

Contents

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1. Introduction

Compartmentation of signalling allows multiple stimuli to achieve diverse cellular responses with only a limited pool of second messengers. This spatial control of signalling is achieved, in part, by cellular structures which bring together elements of a particular cascade. A prime example in the adult cardiac myocyte is the dyad where juxtaposition of L type Ca^{2+} channels in the sarcolemmal membrane and RyR in the sarcoplasmic reticular membrane permits efficient and tightly-regulated Ca^{2+}-induced Ca^{2+} release. Another membrane structure which is of key importance in the spatial control of signalling in the cardiac cell is the caveola. In this review we will consider the evidence for caveolae as local signalling domains, based on their protein and lipid profiles and distinct morphology, with a focus on cAMP, NO and Ca^{2+}.

1.1. Caveolae

Caveolae were first described in endothelial cells by Palade in the 1950s as membrane invaginations and sub-membrane vesicles 50–100 nm in diameter [1]. They are a type of lipid raft, a liquid-ordered domain of the membrane enriched in cholesterol and sphingolipids [2] (see Fig. 1). The key feature which distinguishes caveolae from other lipid rafts is the presence of caveolin; caveolins are 18–22 kDa proteins which insert asymmetrically into the plasma membrane in a hairpin-like conformation, with both N and C termini found intracellularly (Fig. 1B). Caveolin is responsible, in part, for the typical flask-like morphology of the caveola through this asymmetrical membrane insertion and its tendency to cluster into oligomers, both of which promote membrane curvature [3]. Within the last decade, another group of proteins, the cavins, have been shown to contribute to caveolar biogenesis and function (see [4] for a recent review).

Caveolae are important in a variety of cellular processes including endocytosis and cholesterol homeostasis, however one of their best characterized roles is as a signalosome, a platform for pre-assembled complexes of receptors, signal components and their targets (e.g. ion channels), which facilitates fast and specific cellular responses. These complexes can be dynamically regulated on an acute timescale to allow, for example, agonist stimulated access of receptors to their effectors [5,6].

1.2. Caveolins

A fundamental aspect of the control of signalling by caveolae resides within the caveolin protein itself. Caveolin exists as 3 major isoforms: Cav1, Cav2 (expressed in most cell types) and Cav3 (designated the 'muscle-specific' isoform, found only in smooth, skeletal and cardiac muscle). Cav1, 2 and 3 are present at the mRNA and protein level in the adult (rat) ventricular myocyte [7–9] (but see [10]). All caveolins contain a highly conserved 20 residue sequence, the caveolin scaffolding domain (CSD) located in the membrane-proximal N terminus (Fig. 1B), which interacts with a complimentary

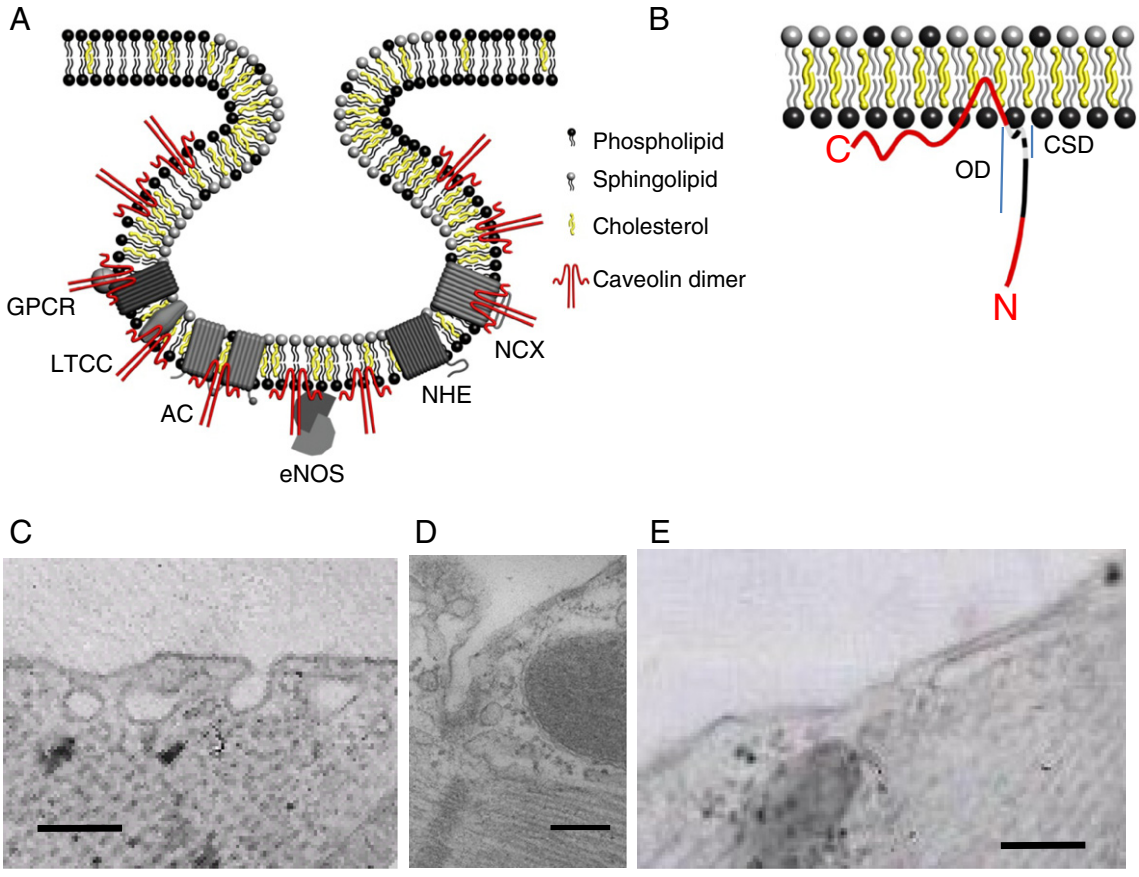

Fig. 1. Caveolae and caveolin. A. Caveolae are invaginated lipid rafts enriched in cholesterol and sphingolipids and lined with the protein caveolin (shown here for simplicity as a dimer, although it normally exists as oligomers of 14–16 caveolins). Within the caveola, some of the key proteins that may be relevant to their function as local signalling domains are shown including G protein coupled receptors (GPCR, with associated G protein), ion channels (e.g. the L type Ca^{2+} channel, LTCC), eNOS, exchangers (NHE and NCX). B. The caveolin protein inserts into the inner leaflet of the membrane. It oligomerises via its oligomerisation domain (OD) and interacts with its binding partners via the caveolin scaffolding domain (CSD). Figures courtesy of Tim Lee, Faculty of Biological Sciences, University of Leeds. C. Caveolae visualised using transmission EM in the adult rat ventricular myocyte; both open and closed vesicles of a size consistent with caveolae are seen. A proportion of closed vesicles may represent open caveolae sectioned outside the plane of the connecting neck region. D. Caveolae are present in t-tubular openings. E. Treatment of myocytes with the cholesterol-depleting agent methyl-β-cyclodextrin (2 mM for 1 h at 37 °C) results in a marked loss of caveolae. Scale bars represent 200 nm.