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Liaison alcaline: Pals entice non-endosomal ESCRTs to the plasma membrane for pH signaling

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The alkaline pH-responsive Pal/Rim signal transduction pathway mediating regulation of gene expression by ambient pH has been extensively studied in *Aspergillus nidulans* and *Saccharomyces cerevisiae.* In *A. nidulans*, PalH, PalI, PalF, PalC, PalA and PalB are required for the proteolytic activation of the executing transcription factor PacC. Although necessary, Pal proteins are insufficient to transmit the signal, which additionally requires ESCRT-I, II and Vps20 with Snf7 in ESCRT-III. Although this initially suggested cooperation between a plasma membrane sensor and an ESCRT-containing Pal complex on endosomes, recent evidence convincingly indicates that pH signaling actually takes place in plasma membrane-associated foci in which Pal proteins and an ESCRT-III polymer scaffold cooperate for pH signaling purposes, representing another non-endosomal role of ESCRT components.

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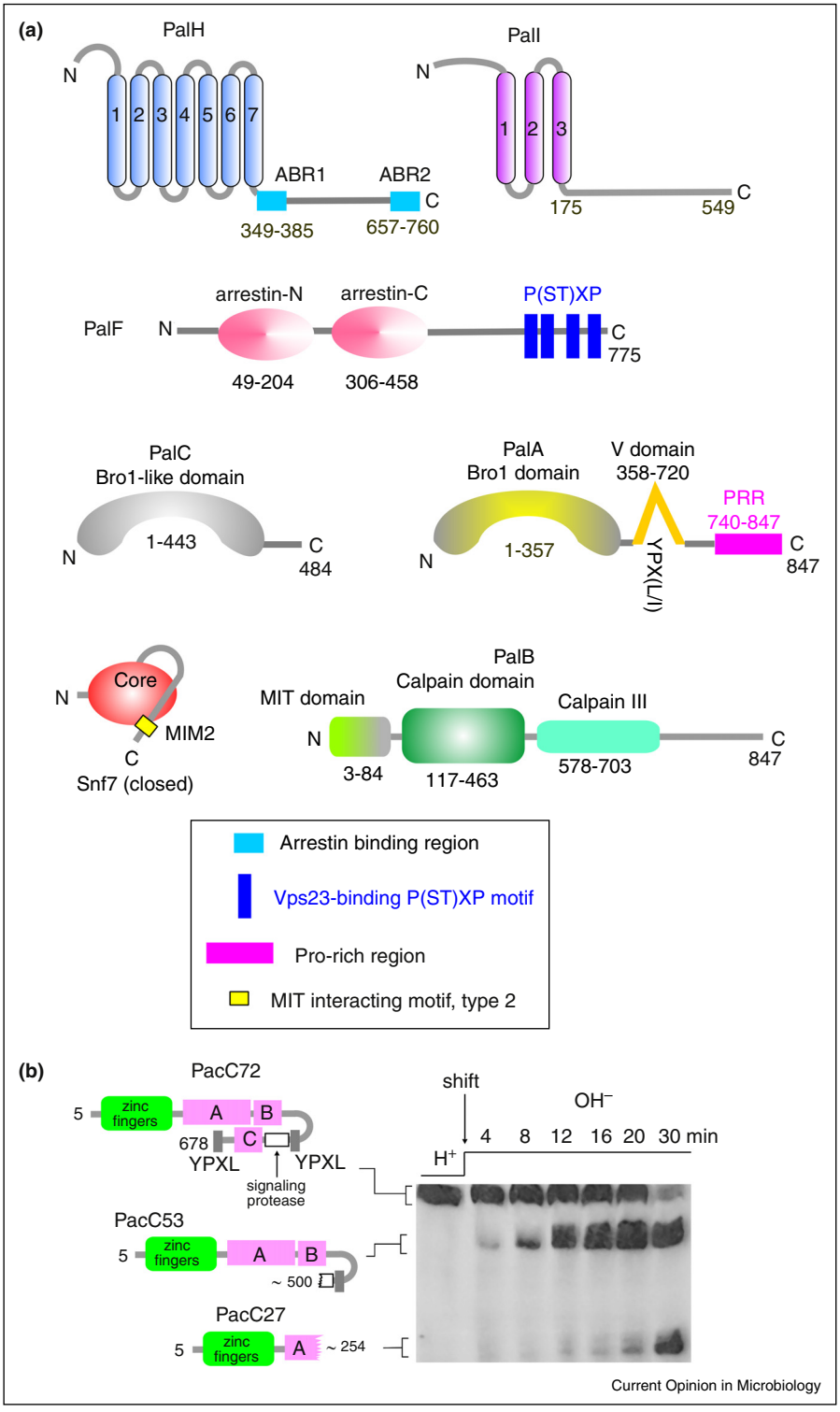
Introduction

The ability to control gene expression in response to ambient pH enables fungi to synthesize gene products, particularly those destined to operate beyond the plasma membrane, in an environmentally appropriate fashion. This ability is of practical importance in a number of contexts, most notably for its crucial role in fungal pathogenicity of both plants and animals. A number of previous reviews have covered both the mechanistic and practical aspects of gene regulation by ambient pH [1–4,5•]. The signaling of ambient pH to an 'executive' transcription factor is a cooperative venture involving dedicated, pH signaling-specific proteins, collectively denoted the Pal pathway in *Aspergillus nidulans* and the Rim pathway in *S. cerevisiae*, and a number of co-opted multivesicular body (MVB) pathway components, the ESCRTs (endosomal sorting complexes required for transport). Most of the recent progress has involved elucidation of the roles of the ESCRTs in *A. nidulans*, where we therefore focus this review. However, we also include important results from *S. cerevisiae* and other fungi, particularly where these cover gaps in the *A. nidulans* data. For simplicity we will refer to ESCRT components using *S. cerevisiae* nomenclature [6].

The Pal pH signaling pathway

The Pal pH signaling pathway is switched on by alkaline pH, which results in the proteolytic processing activation of the transcription factor PacC mediating transcriptional adaptive responses to environmental pH changes. Before proceeding it is necessary to describe briefly the properties of the six dedicated pH signaling (Pal) proteins (Figure 1a) and the three-zinc finger transcription factor PacC (Figure 1b) (In order to keep track of the large number of genes/proteins involved in ambient pH regulation, readers are urged to refer to the figures frequently). We describe these in the order in which they participate in the signaling pathway. PalH is a seven trans-membrane domain (TMD) protein localizing to plasma membrane and containing two cytosolic C-terminal domains that interact with PalF [7,8•,9••]. PalH is probably the pH receptor. PalH is probably the pH receptor. PalI, a three TMD protein localizing to the plasma membrane, is largely necessary for PalH plasma membrane localization and might form a plasma membrane complex with PalH [8•]. PalF is an arrestin-like protein, containing typical N- and C-terminal arrestin domains, which enables signaling from the PalH receptor to which it binds [9••]. PalC and PalA contain a Bro1 domain that characteristically interacts with ESCRT-III Snf7 [10•]. PalC consists of a Bro1-like domain virtually covering its entire length [11,12••]. PalA is remarkably similar to the mammalian protein ALIX [13•,14•]. Like the latter, PalA contains an N-terminal Bro1 domain followed by a 'V-shaped' domain involved in interaction with YPX(L/I) motifs in the PacC transcription factor and a Pro-rich region (PRR) (Figure 1a). PalB is a cysteine protease of the calpain family, containing two calpain domains as well as an N-terminal MIT domain that recognizes ESCRT-III components (see below) [15,16]. Snf7 is the most abundant component of the ESCRT-III polymer. It is synthesized in a 'closed' auto-inhibited conformation. Snf7 is able to

Figure 1



Key players in the Pal signaling pathway. **(a)** Domain organization of Pal proteins and Snf7: the six Pal proteins and Snf7, the main component of the ESCRT-III polymer (shown is the closed, monomeric conformation) are displayed schematically (see text for details). **(b)** Proteolytic processing activation of PacC72. At left, the three forms of PacC with the zinc finger region [66] and the intra-molecular interaction regions A, B and C [67] indicated. N- and C-terminal residues are indicated for each form with Met5 being N-terminal [19,68]. At right, western blot monitoring N-terminally tagged PacC upon transfer of mycelia from an acidic to an alkaline medium.