

Langerin/CD207 Sheds Light on Formation of Birbeck Granules and Their Possible Function in Langerhans Cells

Jenny Valladeau¹
Colette Dezutter-Dambuyant¹
Sem Saeland²

¹INSERM U346, Hôpital
Edouard Herriot, Lyon, France

²Laboratory for Immunological
Research, Schering-Plough,
Dardilly, France

Abstract

Langerhans cells (LCs) are immature dendritic cells of epidermis and epithelia, playing a sentinel role through their specialized function in antigen capture, and their capacity to migrate to secondary lymphoid tissue to initiate specific immunity. A unique feature of LCs is the presence of Birbeck granules (BGs), which are disks of two limiting membranes, separated by leaflets with periodic “zipper-like” striations. The recent identification of Langerin/CD207 has allowed researchers to decipher the mechanism of BG formation and approach an understanding of their function. Langerin is a type II lectin with mannose specificity expressed by LCs in epidermis and epithelia. Remarkably, transfection of Langerin cDNA into fibroblasts creates a dense network of membrane structures with features typical of BGs. Furthermore, mutated and deleted forms of Langerin have been engineered to map the functional domains essential for BG formation. Langerin is a potent LC-specific regulator of membrane superimposition and zippering, representing a key molecule to trace LCs and to probe BG function.

Key Words

Langerhans cells
Birbeck granules
Tectin
Endocytosis
Membrane plasticity

Introduction

Langerhans cells (LCs) are characterized *in situ* by the presence of long and fine cytoplasmic extensions emerging from small cellular bodies. Traditional stainings used in histology do not differentiate LCs from surrounding keratinocytes. The use of histochemical (gold salts) and histoenzymatic

(adenosine triphosphatase or myeloperoxidase) methods made it possible to locate the LCs in basal and suprabasal layers of the skin. By electron microscopy, Birbeck et al. (1) subsequently characterized their ultrastructure. LCs have a lobulated nucleus surrounded by a clear cytoplasm devoid of tonofilaments, desmosomes, or melanosomes. However, they possess a unique intracytoplasmic organelle that is

their characteristic ultrastructural feature: the Birbeck granule (BG) (*1*; Fig. 1).

Morphology of BGs

The BG presents as a linear or curved rod, often with a so-called tennis racket shape when one of its ends is in continuity with a vesicle (Fig. 1B). The BG is formed by two joined membranes, separated by a regularly striated zone (periodicity of 5–10 nm). Seldom-observed transverse sections present a checkerboard pattern formed by electron-dense and electron-clear particles (*2*). The three-dimensional structure of BGs was established by serial observations of ultrathin sections and confirmed by scanning microscopy after cryofracture (*3*). By compilation of different sections, the BG resembles a disk-shaped structure (1 μm in diameter and approx 50 nm thick), with a spherical vesicle-like formation at one of its ends (*4*; Fig. 1C).

Intracellular Localization of BGs in LCs

BGs are often observed in the perinuclear area close to the Golgi region or attached to the plasma membrane in continuity with the extracellular space where they are also called “cytoplasmic sandwiching structures,” precursors of BGs, or “Birbeck granule-like structures.” Rare micrograph images also show accumulation of BGs around the centriole or in contact with microtubules (*5*). In more recent studies using videomicroscopy, Velleca (*5*) suggest that BGs move from the cell periphery toward the pericentriolar area along microtubules. Quantification studies carried out by Bartosik et al. (*6*) show that a human LC displays a minimum of approximately 100 BGs.

Formation of BGs

In addition to LCs located in suprabasal layers of the epidermis and in an intraepidermal position, some cells present in dermis, and, more rarely, veiled dendritic cells (DCs)

and interdigitated DCs, can have BGs (*7–9*). BGs can be considered as a specific marker of LCs migrating or entering secondary lymphoid organs. However, most interdigitating DCs, and LCs isolated and maintained in culture with granulocyte macrophage colony-stimulating factor (GM-CSF), no longer present BGs (*10*).

LCs treated with detergents such as sodium lauryl sulfate (*11*) or digitonin (*12*), which are known to act on membrane plasticity, increase the number of BGs in continuity with the plasma membrane. In such conditions, the periodic striation characteristic of BGs is preserved although their overall shape is modified. Granules present a larger size, are sometimes circular, display a U shape, or have two vesicles at their ends. Topical treatment with haptens such as DNFB (*13*) or irritants such as dithranol (*14*) produce the same effect.

Moreover, although BGs are restricted to LCs in normal conditions, they can also be observed in other cell types in nonphysiologic conditions. Thus, structures related to BGs and connected to the plasma membrane are described in leukemic cells (*15*) and in platelets in the presence of EDTA. In platelets, the formation of these structures is likely induced by the dissociation of $\alpha\text{IIb}\beta 3$ integrins (*16*). However, a different phenomenon is observed when LCs are incubated with EDTA. Indeed, this agent induces a dissociation of BGs or a dezippering of the structure, leading to a reduction in BG numbers, which suggests different mechanisms of action of EDTA in LCs and platelets, and underlines the importance of calcium in the maintenance of BG integrity (*17*).

In the mouse, in addition to BGs, related structures named “cored tubules” are observed (*18*). Similarly described in cells isolated from dermis (*19*) or lymph nodes (*20*), cored tubules form a network of bilamellar structures with various shapes, thinner than the characteristic BGs, and devoid of paracrystalline formation.