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Preface

From rags to riches — The history of the endoplasmic reticulum

The first scientist to view the cell was the English natural philosopher, architect and polymath Robert Hooke in 1665 [30]. The information gleaned from his visual analysis of cells was limited to the level of resolution offered by the technology of his time. Thus, it took nearly two centuries until researchers started to realize that the cellular building block of the organism is itself subdivided into conserved structures. This critical turning point was catalyzed by the development of more sophisticated microscopes, in conjunction with novel staining methods that increased the contrast within the sample. The first such defined intracellular structure to be discovered was the nucleus. First described by the microbiologist Antony van Leuwenhook and the botanical artist Franz Bauer, the nucleus was studied in detail and named by the Scottish botanist Robert Brown in 1833 [11]. Soon after, in 1857, the Swiss zoologist, Albert von Kölliker and others, described an additional structure in muscle cells that was later named mitochondria by Carl Benda [6]. The series of newly described organelles continued with the identification of chloroplasts in 1883 by Andreas Franz Wilhelm Schimper [26,29] and the Golgi apparatus in 1897 by the Italian pathologist Camillo Golgi [7]. Hence the 19th century constituted the golden era of organelle discovery.

Because the living cell was structurally and functionally subdivided into entities with a clear analogy to body organs, in 1884 the German Zoologist Karl August Möbius suggested the name “Organellula” [18]. The term was readily accepted, eventually changed to ‘organelle’ and expanded in meaning to include subcellular structures in both unicellular and multicellular organisms. Despite this eruption of knowledge enabled by scientists from various countries, one central organelle remained offstage until late in the first act.

The endoplasmic reticulum (ER) is one of the largest, most functionally complex and architecturally varied organelles within the cell. Despite this, it was one of the last big organelles to be described. The ER was discovered in 1902 by careful observations of the Italian scientist Emilio Veratti [16,31]. As a student of Golgi, Veratti used Golgi's staining procedures and found a new subcellular structure that he could verify to be distinct from the filaments of the muscle and the Golgi apparatus [31]. Despite Veratti's careful observations and drawings he could never convince the contemporary scientific community that such an organelle existed. In fact, his work was disregarded and put away, thus, while research on the Golgi apparatus (see Fig. 1) and other organelles was dashing forward, the ER was left behind. In retrospect, it is difficult to explain how, in an era of excitement and interest in sub-cellular structures, this organelle was slow to be acknowledged. In fact, it was a technological advance again that enabled the rediscovery of the ER. In 1953, Keith Porter developed electron microscopy (EM) techniques that allowed him to observe a net-like (reticulum) structure within (endo) the cytoplasm (plastic). He therefore named the structure endoplasmic reticulum [24]. The final stamp of approval came in 1954 when Porter teamed up with the father of modern cell biology, George Palade, and together, they obtained high-resolution images and finally proved the existence of this organelle [22]. And so, over 50 years after its discovery, the ER stepped into the limelight and was accepted as a *bona fide* organelle, attracting much curiosity and becoming the object of many investigations.

A major contribution to the study of the ER came with a protocol published by Palade outlining a method to isolate ER-derived “microsomes”, a cell fraction in which the extensive ER network has become mechanically sheered into tiny, sealed vesicles [23]. The possibility to perform biochemical assays on purified organelle fractions in combination with microscopy-based analyses opened the door to amazing discoveries as to the function, structure and composition of this recently identified organelle. By the early 1960s, the role of the ER in muscle contraction and its essential role in calcium sequestration was proven [16]. These discoveries made studies on the mechanisms by which the ER sequesters and releases Ca^{2+} a major field that would shape our understanding of muscle contraction, signaling, fertilization and neurotransmission. At the same time, it was demonstrated that lipid biosynthesis also takes place at the ER [28].

Already in the early EM pictures it was obvious that the ER membrane is studded with ribosomes providing the first evidence that it is the site of entry into the secretory pathway. This was then elegantly demonstrated using a combined EM and autoradiography approach to visualize the flow of proteins from the cytosol, through the ER and onwards to the Golgi on their way to secretion [3]. Work initiated by Günter Blobel in 1971, using a cell free protein synthesis system, enabled experiments seeking to answer the puzzling riddle of how proteins enter the ER. Soon it became clear that signal sequences are utilized as “zipcodes” to target proteins [2,14,15,17] and later the machinery that recognizes them was defined and named the signal recognition particle (SRP) [32]. In parallel to these biochemical approaches the realization that the genetically pliable baker's yeast can be used to study secretion boosted the field with the discovery of a large number of mutants that halt secretion at various stages [21]. An interesting subclass of mutants were those that specifically affected protein's entry into the ER, “translocation” [5]. Study of these mutants with the aid of biochemical approaches [9,13] enabled the discovery of the translocon itself. These discoveries laid the foundation for a mechanistic understanding of translocation.

As elegant biochemical assays for trafficking became available [1] and following the discovery of the major folding [20], protein disulfide isomerization [8], and glycosylation pathways of the ER [10,12,25], a true understanding of the processes required for secretion began to be elucidated. It soon became clear that secretion is quality controlled, i.e. that proteins only exit the ER after they have reached their native tertiary and quaternary state.

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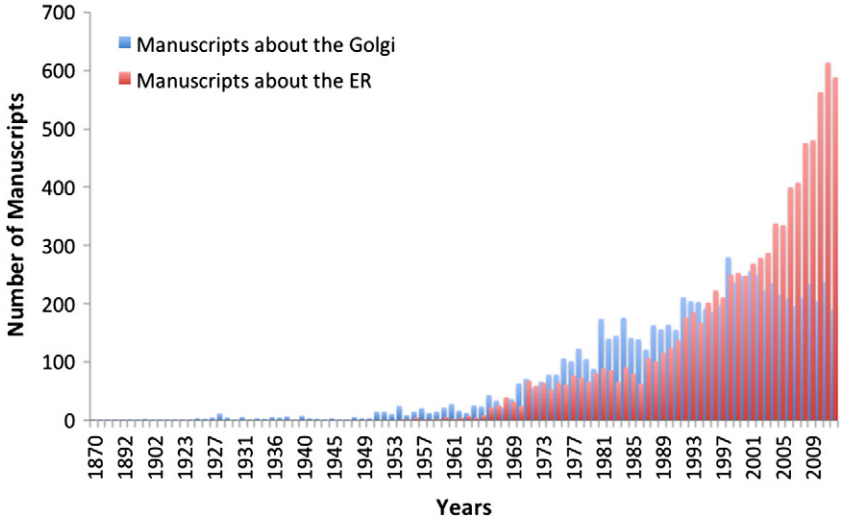

Fig. 1. The number of manuscripts published each year since the discovery of each of the two organelles — the Golgi apparatus (since 1898) and the endoplasmic reticulum (ER) (since 1902).

As the field of ER studies was maturing, two major discoveries propelled it into the limelight of a vast number of cell biological explorations: the characterization of the machineries required for the unfolded protein response (UPR) [4,19,27] and ER associated degradation (ERAD) (see the historic review on ERAD in this issue). The identification of these two pathways brought about the understanding that each step of protein secretion is tightly regulated and controlled: proteins don't just "flow" through the ER, rather this organelle plays an active role in the folding, assembly and posttranslational modification of secretory proteins. This brought about a wave of studies focusing on how ER functions take part in controlling development and highlighted the link between ER misregulation and a large variety of diseases ranging from diabetes to cancer. Interestingly, in correlation with the discovery of the UPR and ERAD, the year 1997 marked a turning point in which the number of manuscripts published about the ER rose above those published about the Golgi apparatus and continues to rise to this day (Fig. 1).

And so, since its discovery more than a hundred years ago the ER has taken its place as a key protagonist in cellular organization and function. Each year reveals new fascinating facets of ER function and regulation as well as the secrets of how it creates and maintains its intricate structure. The last decade has also demonstrated that the ER plays a central role in inter-organelle communication by hosting contact sites with all other intracellular organelles. With the advent of systematic approaches to biological processes and the development of the field of functional genomics, studies on ER function and homeostasis have progressed even faster. However, more than half of ER proteins are poorly characterized indicating that many exciting years of discovery still lie ahead. This issue on many of the functions of the ER is a celebration to this unique organelle that serves as a hub for folding, lipid biosynthesis, ion homeostasis and intracellular communication between organelles.

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