Regulation of Golgi unlinking during G2/M transition

The Golgi complex (GC) of mammalian cells is composed of stacks of cisternae connected by membranous tubules to create a continuous network, the Golgi ribbon, whose maintenance requires several core and accessory proteins. Despite this complex structural organization, the GC is highly dynamic. This property becomes particularly evident during mitosis, when the ribbon undergoes a multistep disassembly process that allows its correct partitioning and inheritance by the daughter cells (1). We have recently revealed a novel mechanism of the Golgi stacking protein GRASP65 in the regulation of Golgi structure (2). In particular, we demonstrate that GRASP65 binds indirectly to Golgi-associated microtubules (MTs), leading to their stabilization and acetylation. This post-translational modification increases the activity of minus-end directed motors, favouring the clustering of Golgi stacks and ribbon formation (2). Ribbon formation and MT acetylation are both regulated by JNK-mediated phosphorylation of GRASP65, suggesting that GRASP65 coordinates Golgi structure with MT organization. In agreement with this role, tubulin acetylation is strongly reduced during the G2 phase of the cell cycle, allowing the “unlinking” of the Golgi ribbon into isolated stacks and consequently, progression into mitosis (2). This activity is specifically associated to GRASP65 and not to other related Golgi proteins (e.g., GRASP55), indicating that the JNK2/GRASP65 axis is crucial for the integration of various stimuli to regulate the organization of GC and MTs in preparation for entry into mitosis (discussed in (2)). Regarding the mechanism, we are setting up a series of different techniques for the identification of GRASP65 interactors. In addition, we have focused on the signalling pathway upstream of S274 of GRASP65. A crucial method has been the development of an antibody raised against human GRASP65 phosphorylated in S274. We tested the effect on this phosphorylation after the treatment with a series of kinase inhibitors and siRNA-mediated knockdown of candidates. By this approach we are delineating a pathway that is composed of PKD2 and FAK, in addition to JNK2 activation through the MAP kinases MAP3K2, MEKK7 and MEKK4.

References:

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