Possible mechanisms of amyloid growth

At present there is no consensus whether a protofilament is formed by joining oligomers or by adding monomers. The following questions can be posed: How many different mechanisms exist in the literature to describe the protein aggregation? What is the essence of each mechanism? What mechanisms or models are used in the literature to describe the experimental kinetic curves? What are the similarities between various mechanisms? The large volume of publications describing the formation of amyloid fibrils allows us to reveal two general mechanisms. There are a mechanism of sequential addition of monomers (linear growth) and a mechanism for describing the aggregation of prions (exponentional growth) (Fig.1). We analyzed two types of regimes of amyloid growth: linear and exponential.

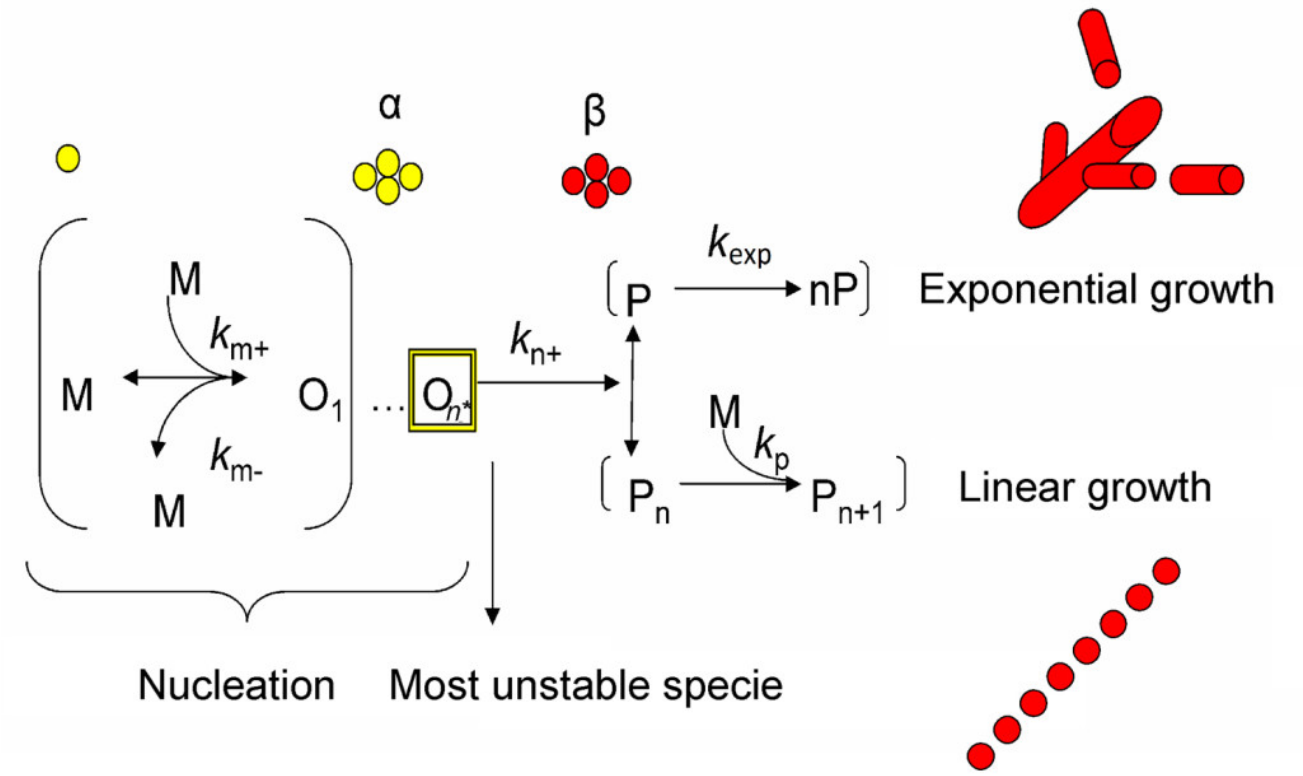

Fig. 1. General scheme for amyloid formation depicting linear and exponential growth models.

Both of the reactions do have a sigmoidal shape of the kinetic curve. However, the difference between the two types is in the relation of the time required to transfer all the protein particles into an aggregate to the lag time. The linear regime is called so because the reaction rate is proportional to the nucleation rate. Linear regime of growth has a very narrow range of conditions, the relation of the time required to transfer all the protein particles into an aggregate to the lag time

does not depend on the concentration and its value cannot exceed 0.2. From the mechanistic point of view, the linear regime of growth is the growth occurring only from ends of the growing rod-like amyloid, i.e. the number of growing ends is proportional to the amount of fibrils. There is a number of amyloid kinetics which cannot be explained from positions of the linear regime mechanism, since the aggregate grows much faster than one can expect according to such a regime. Such kinetic behavior can only be explained if one assumes extra “boosting” steps, like fragmentation and growth from the surface or branching (Fig.2).

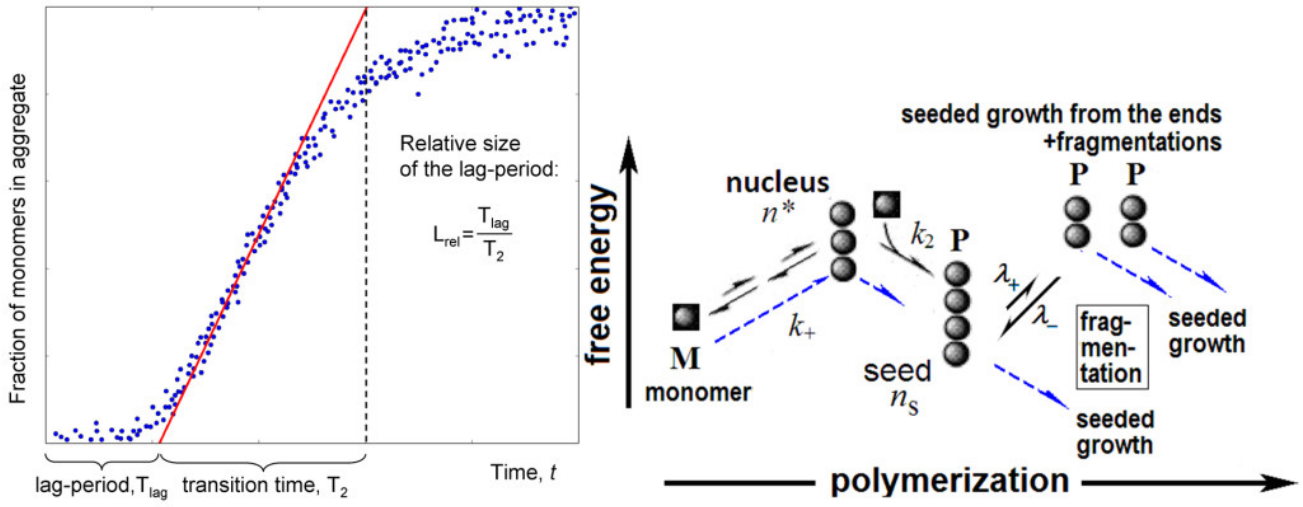

Fig. 2. Typical kinetic curve for the exponential process of amyloidogenesis with characteristic times. Dependence of the free energy on the reaction coordinates in the process of amyloidogenesis with fragmentations.

In order to estimate the size of fibril nucleus (the most unstable state on the monomer to the fibril pathway) and a possible scenario for formation of aggregates, it is necessary to make a number of kinetic experiments, where the only variable parameter is the monomer concentration. Characteristic times T_{lag} (the lag-period duration), T_2 (the time of transition of all monomers into an aggregate) and L_{rel} (the T_{lag}/T_2 ratio) are calculated for each experimental curve (Fig.2). It was demonstrated that the dependences of $\ln T_2$ and L_{rel} on the logarithm of the initial concentration of monomers are linear, with gradients that can be used for computation of fibril nucleus sizes (including those of non-amyloid type) and for elucidation of the mechanism of aggregate formation. If $L_{rel} > 0.2$, the linear growth model is excluded and only the exponential growth scenario remains. The dependences of $\ln T_2$ and L_{rel} on the logarithm of the initial concentration of monomers are formally different for different exponential scenarios (i.e., “growth from the surface”, “fragmentation” and “bifurcation”). However, it is impossible, e.g., to distinguish the bifurcation from the fragmentation scenario from the kinetics *alone* if the size n_2 of the secondary nucleus of bifurcation is zero; this implies the need for direct observations of fibril shapes to distinguish these

cases.

Oxana V. Galzitskaya, Elena I. Leonova, Nikita V. Dovidchenko
Institute of Protein Research, Russian Academy of sciences

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