Gametogenesis in Plasmodium.

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Plasmodium
gamete
ookinete
invasion
mosquito
magot

Résumé : **Gametogenèse de Plasmodium.**

L'organisation subcellulaire et moléculaire de la gametogenèse du Plasmodium *demeure un des événements les plus dramatiques dans le cycle vital du parasite, tant en ce qui concerne la rapidité du développement cellulaire que son organisation délicate. Cet article fournit un bref résumé de ces événements ainsi que des progrès récents dans notre compréhension des processus régulatoires qui en contrôlent le développement.*

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In the understandable drive to focus on the protection of the individual malaria infected human host from death or morbidity, persons wishing to control or contain malaria often overlook past practical experiences that the parasite is most susceptible to intervention as it passes through the mosquito vector.

Following the early recognition in the 1890's that the sexual stages (gametocytes) are uniquely responsible for transmission of the parasite to the mosquito, it was some 80 years before the true wonder of the sub-cellular biology underlying sexual differentiation began to be appreciated. Whilst we are still totally ignorant of the processes that trigger sexual development, the subsequent differentiation of gametocytes is now being unravelled, nevertheless in P. *falciparum* none of the known molecular markers yet distinguishes the committed sexual parasite before it is morphologically recognisable as a stage I or II gametocyte (i.e. day 2 of development). Importantly, the mature gametocytes are now recognised as being pre-committed but arrested in Go of the cell cycle. Due to this arrest they are insensitive to most inhibitors of macromolecular biosynthesis, but remain sensitive to inhibitors of energy metabolism. This has important implications for the design and implementation of effective chemotherapy which should have the important aim of blocking infectivity to the vector.

Factors regulating the resumption of the sexual cell cycle when the gametocytes are taken into the mosquito vector are complex and include : extracellular pH, temperature, and the gametocyte activating factor-recently identified as xanthurenic acid. Current studies have shown how these factors are modulated by asexual parasitaemia, chemotherapy and in the case of xanthurenic acid by mosquito genotype.

Following induction, gametogenesis is initiated, this dramatic and rapid differentiation has been comprehensively described at the ultrastructural level, but the molecular organisation remains largely unexplained, e.g. How does the parasite replicate its entire genome 3 times in less than 10 minutes? Why don't the chromosomes condense during each of the 3 mitotic divisions of microgametogenesis? What regulates the highly ordered intracytoplasmic assembly of the 8 flagellar axonemes of the male gametes? Clearly the parasite has solutions to well studied cellular events, that have not yet been described in any other eukaryotic cell. When resolved these events should be expected to be vulnerable to as yet unknown specific inhibitors. Amongst these may be naturally derived products related to azadirachtin.

Following gametogenesis the gametes fuse, but we do not yet know whether there is any tactile response of the motile male to the female gamete. Fertilization follows in an environment that is essentially the vertebrate blood containing largely lysed erythrocytes. This environment is changed over the next 24 hours by the digestive enzymes of the mosquito vector. During this time the vertebrate immune system is progressively compromised, however antibodies clearly survive at effective levels and can be transported intact into the mosquito haemocoele. Our understanding of these changes is critical to the design of effective transmission-blocking vaccines targeted to the gamete/zygote or the ookinete stages. Such vaccines are now at an advanced stage of development. Whilst the biological roles of the target molecules are unknown evidence will be presented to show that the recent availability of genetic knockout technology will assist in this effort.

Further evidence of the vital interplay between the parasite and vector is shown by mechanism by which ookinete penetrates the peritrophic matrix. The parasite secretes an inactive prochitinase that is activated by mosquito trypsin to form chitinase which then disrupts the matrix permitting passage of the ookinete.

Whilst penetration of the gut wall by the ookinete is now well studied at the microscopic level, the molecular basis for this interaction remains unknown. Some studies are interpreted to suggest selected cell types are invaded, but these studies have not however adequately resolved the question as to whether the observations describe the midgut cell phenotype before invasion, or after invasion when significant pathology occurs. In the midgut wall the ookinete clearly triggers the insects immune defence mechanisms e.g. Gram negative binding protein and defensin production, ookinete lysis and melanisation. The genetic basis for these mechanisms when elucidated could provide further novel strategies for intervention using transgenic vectors.

We are now beginning to recognise that the biology of the malaria parasite in the mosquito, and its interactions with both the vertebrate host (bloodmeal) and insect vector is every bit as complex as development in the human host, but much more fascinating at the sub-cellular levels. If correctly and rationally analysed we can, on past evidence, expect the data will contribute significantly to the eventual containment of the parasite.