

Kratek opis usposabljanja mladega raziskovalca (*Short description of the Young Researcher's training*)

1. Raziskovalna organizacija (*Research organisation*):

Medicinska fakulteta, Univerza v Ljubljani, Inštitut za patološko fiziologijo / Faculty of Medicine, University of Ljubljana, Institute of pathophysiology

2. Ime, priimek in elektronski naslov mentorja (*Mentor's name, surname and email*):

Nina Vardjan, nina.vardjan@mf.uni-lj.si

3. Šifra in naziv raziskovalnega področja (*Research field*):

3. Medicina (3.03. Nevrobiologija) / 3. Medicine (3.03. Neurobiology)

4. Kratek opis usposabljanja mladega raziskovalca (*Short description of the Young Researcher's training*):

Navedite tudi morebitne druge zahteve, vezane na usposabljanje mladega raziskovalca (npr. znanje angleškega jezika, izkušnje z laboratorijskim delom, potrebne licence za usposabljanje...).

Raziskovalno delo mladega raziskovalca bo potekalo na Inštitutu za patološko fiziologijo Medicinske fakultete v Ljubljani v okviru financiranja ARRS MR+. Začetek raziskovalnega dela je predviden v jeseni 2019.

Vsebina raziskovalnega dela

Raziskovalno delo mladega raziskovalca bo vključevalo raziskave fiziologije astrocitov, ne-nevronske celice glave, ki v centralnem živčnem sistemu (CZS) predstavljajo heterogeno populacijo celic s številnimi funkcijami, med drugim astrociti modulirajo aktivnost nevronov in presnovo CZS.

Čeprav električno nevzdražni, se lahko astrociti preko z G-proteini sklopljenih receptorjev (GPCR) odzovejo na zunajcelične signale s citoplazemsko vzdražnostjo. Le-ta se kaže kot sprememba v koncentraciji znotrajceličnih sekundarnih prenašalcev (Ca^{2+} , cAMP), kar vpliva na številne procese, tudi presnovo astrocitov. Astrociti privzemajo glukozo iz krvnega obtoka ter jo skladiščijo v glikogenu. Ko narastejo potrebe po energiji aktivacija GPCR na površini astrocitov povzroči pospešeno presnavljanje shranjene glukoze v astrocitih, ki se v procesu aerobne glikolize pretvarja v laktat in izloča iz astrocitov. Laktat lahko vstopa v nevrone, kjer se porablja kot vir energije. Ta presnovna povezava med astrociti in nevroni je pomembna za oblikovanje spomina.

Ugotovljeno je bilo, da v možganih pri različnih nevrološki obolenjih (npr. nevrodegeneraciji) prihaja do presnovnih motenj. V zgodnjih fazah Alzheimerjeve bolezni je bil ugotovljen hipometabolizem, ki se pojavi še pred znaki demence. Kakšno vlogo imajo pri tem astrociti še ni znano. Namen dela mladega raziskovalca je ugotoviti ali med nevrodegeneracijo pride do sprememb v GPCR-posredovanem uravnavanju znotrajceličnih signalnih poti in v presnovi astrocitov, kar bi vplivalo na presnovno podporo astrocitov nevronom in prispevalo k nastanku/napredovanju nevrodegenerativnih bolezni. Raziskava ima translacijski potencial, saj bodo izsledki raziskave morda razkrili nove tarče za zdravljenje nevrodegeneracije.

Metode dela

Mladi raziskovalec bo izvajal meritve znotrajceličnih sekundarnih prenašalcev in metabolitov v astrocitih po aktivaciji receptorjev GPCR. Pri tem bo uporabljal fluorescenčne označevalce in pa genetsko kodirajoče nanosenzorje in visokoločljivo fluorescenčno mikroskopijo v realnem času. Meritve bo izvajal v posameznih astrocitih v i) kulturi (*in vitro*), ii) tkivnih možganskih rezinah (*in situ*) izoliranih iz živali

divjega tipa in modelnih živali nevrodegenerativnih bolezni (glodalci) oz. iii) *in vivo* v možganih živali divjega tipa in modelnih živali nevrodegenerativnih bolezni (*Drosophila melanogaster*).

Kandidate, ki bodo do predvidenega roka septembra 2019 zaključili magistrski študij na 2. stopnji naravoslovnih smeri kot so biologija, biokemija, medicina, biotehnologija, mikrobiologija, farmacija, kemija in imajo željo po raziskovanju vabimo, da pošljejo življenjepis in motivacijsko pismo na naslov: nina.vardjan@mf.uni-lj.si. Prednost pri izbiri bodo imeli kandidati z visoko povprečno oceno študija in izkušnjami z delom v celični biologiji in biokemiji/molekularni biologiji.

eng:

The research work of a young researcher will be carried out at the Institute of Pathophysiology of the Faculty of Medicine in Ljubljana and funded by the Slovene Research Agency MR+ program. The beginning of the research work is planned for autumn 2019.

Content of the research work

The research work of a young researcher will involve research of astrocyte physiology. Astrocytes are non-neuronal glia cells, which in the central nervous system (CNS) represent a heterogeneous population of cells with many functions, including modulation of neuronal activity and CNS metabolism.

Although electrically silent, astrocytes via G-protein coupled receptors (GPCRs) respond to extracellular signals with cytoplasmic excitability. This is seen as a change in the concentration of intracellular second messengers (Ca^{2+} , cAMP), what affects many processes, including astroglial metabolism. Astrocytes uptake glucose from the bloodstream and store it in the form of glycogen. When energy requirements in the CNS increase, activation of GPCRs on the surface of astrocytes results in accelerated glucose metabolism in astrocytes, which causes conversion of stored glucose into lactate in the process of aerobic glycolysis. Lactate is then released from astrocytes and can enter neurons, where it is used as an energy source. This metabolic interplay between astrocytes and neurons is important for memory formation.

It has been reported that brain metabolism in various neurological disorders (e.g. neurodegeneration) is altered. In the early stages of Alzheimer's disease, hypometabolism has been identified occurring even before the dementia. The role of astrocytes in development of hypometabolism is not yet known. The purpose of the study of a young researcher is to determine whether there is a change in the GPCR-mediated regulation of intracellular signalling pathways and energy metabolism in astrocytes during neurodegeneration, which would affect the metabolic support of neuron by astrocytes and contribute to the onset/progression of neurodegenerative diseases. The research has a translation potential, as the findings of the research may reveal new targets for the treatment of neurodegeneration.

Methods

A young researcher will perform measurements of intracellular second messengers and metabolites in astrocytes upon activation of GPCR receptors, using fluorescence markers, genetically encoded nanosensors and real-time high-resolution fluorescence microscopy. Measurements will be performed in individual astrocytes in i) culture (*in vitro*), ii) tissue brain slices (*in situ*) isolated from wild-type animals and model animals of neurodegenerative diseases (rodents), or iii) *in vivo* in the brain of the wild-type animals and the model animals of neurodegenerative diseases (*Drosophila melanogaster*).

Candidates who will complete the Master's studies of natural sciences by the scheduled deadline of September 2019, such as Biology, Biochemistry, Medicine, Biotechnology, Microbiology, Pharmacy, Chemistry, and who wish to become researchers are invited to send a CV and a motivation letter to the address: nina.vardjan@mf.uni-lj.si. Priority will be given to the candidates with a high average grade of study and with the working experience in the field of cell biology, biochemistry/molecular biology.