1. Raziskovalna organizacija (*Research organisation)*:

Univerza v Ljubljani, Medicinska fakulteta *(University of Ljubljana, Faculty of Medicine)*

2. Ime in priimek mentorja (*Name and surname of a mentor*):

Nina Zidar

3. Področje znanosti iz šifranta ARRS (*Primary research field*):

3 Medicina *(Medicine)*
3.01 Mikrobiologija in imunologija *(Microbiology and Immunology)*
3.04 Onkologija *(Oncology)*

4. Kontaktni e-naslov mentorja (*Contact of a mentor)*:

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5. Kratek opis programa usposabljanja (*Short description of the program)*:

Patogeneza fibroze in stenoze pri kronični vnetni črevesni bolezni.

Fibroza in stenoza sta pomembna zapleta kronične vnetne črevesni bolezni (KVČB) s resnimi kliničnimi posledicami, ki se pomembno razlikujejo med obema oblikama KVČB, ulceroznim kolitisom (UC) in Crohnovo boleznijo (CB). Sodobno zdravljenje je usmerjeno v vnetje, malo napredka pa je prineslo pri preprečevanju in zdravljenju fibroze in stenoze.

Eden od glavnih razlogov za neuspešno zdravljenje fibroze in stenoze je predvsem slabo poznavanje njune patogeneze. V naši raziskavi bomo zato preučevali histološke značilnosti fibroze in stenoze pri KVČB in skušali razložiti, kateri patogenetski mehanizmi so vpleteni v njihov razvoj.

Predpostavljamo, da sta fibroza in vnetje pri UC omejeni na mukozo in submukozo, se ne širita v globje plasti črevesne stene in zato mezotelijske celice niso aktivirane. Pri CB sta fibroza in vnetje transmuralni, zato so mezotelijske celice aktivirane, s posledično aktivacijo miofibroblastov in prekomerno sintezo kolagena, kar vodi v razvoj brazgotine (fibroze) in stenoze.

V prvem delu raziskave bomo preučevali distribucijo fibroze in miofibroblastov v operacijskih preparatih kolona pri bolnikih z UC in CB. Uporabili bomo trikromno barvanje za prikaz fibroze, imunohistokemijo (gladkomišični aktin, erg) za prikaz fibroblastov in miofibroblastov ter mezotelnih celic (npr. kadherini, Snail). Analizirali bomo tudi citokine, zlasti najmočnejši profibrogeni citokin transformirajoči faktor β (TGF β) in mikroRNA, zlasti tiste, za katere je znano, da sodelujejo pri epitelijsko-mezenhimskem prehodu (npr. mikroRNA družine 200).

V drugem delu raziskave bomo skušali našo hipotezo potrditi na kulturi mezotelijskih celic. Natančen protokol tega dela raziskave bo odvisen od rezultatov prvega dela.

Pathogenesis of fibrosis and stenosis in inflammatory bowel diseases

Fibrosis and stenosis are important complications of inflammatory bowel diseases (IBD) with serious clinical consequences, but with significant differences between the two forms of IBD, ulcerative colitis (UC) and Crohn's disease (CD). A significant progress has been made in the treatment of IBD, mainly targeting inflammation. In contrast, little progress has been made in the treatment of fibrosis and stenosis.

One of the reasons for poor success in the treatment of fibrosis and stenosis in IBD is that their pathogenesis is poorly understood. We will therefore analyse histologic features of fibrosis and stenosis in IBD to reveal its pathogenesis.

Our hypothesis is that fibrosis and inflammation in UC are limited to mucosa and submucosa, not extending to deeper layers of the bowel wall. Consequently, there is no activation of mesothelial cells. In CD, fibrosis and inflammation are transmural. Transmural inflammation results in activation of mesothelial cells and proliferation of activated myofibroblasts, with excessive collagen production leading to scar formation (fibrosis) and stenosis.

In the first part of the study, we will analyse the distribution of fibrosis in colon resection specimens from patients with CD and UC, using trichrome staining, distribution of fibroblasts and myofibroblasts using immunohistochemistry for smooth muscle actin, and immunophenotype of mesothelial cells (cadherin, Snail, etc). We will also analyse the distribution and intensity of cytokine expression, particularly transforming growth factor β (TGF β), the most potent profibrogenic cytokine, and expression of microRNAs which are known to induce epithelial-mesenchymal transition (e.g., microRNA of the 200 family).

In the second part of the study, we will try to confirm our results on the culture of mesothelial cells. The exact study design depends on the result of the first part of the study.